Iron Deficiency in Childhood: Causes and Consequences for Child Development

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Key Words
Child development • Cognition • Motor development • Iron deficiency anaemia

Abstract
The main causes of iron deficiency (ID) are briefly discussed, followed by the examination of studies of ID and child cognitive and motor development and behaviour for evidence of a causal link, classifying them by study design. Iron deficiency anaemia (IDA) is associated with many psychosocial and economic disadvantages that can affect child development and could explain the frequently demonstrated relationship between IDA and poor development and behavioural differences. There is evidence of changes to brain function in infants with IDA. Many treatment trials lack statistical power due to small samples, including children without ID in the sampling or iron treatment resulting in little or no differences in iron status between placebo and treated groups. In children with IDA under 3 years, randomized trials indicate that iron supplementation is usually beneficial to motor development, but the effect on mental development is inconsistent. Iron supplementation also has a beneficial effect on cognitive function in school-aged children with IDA. Evidence for a threshold level of ID at which child development is affected is inconsistent, but children with IDA are most likely to benefit from iron supplementation. Possible harmful effects of iron supplementation in iron-replete children on growth and morbidity have to be considered when developing programmes and policy.

It is estimated that 47% of preschool children are anaemic globally and around 50–60% of anaemia cases are due to iron deficiency (ID) [1]. In some poor developing countries, the prevalence of anaemia is over 60% [2]. Thus, the extent to which ID may affect children's development has major implications both for the individual and national development. In this paper, we will briefly discuss causes of ID. Then we will focus on the effects of ID on child development.

Causes of ID

Full-term healthy infants with a normal birth weight have sufficient iron reserves from birth for their requirements for around the first 4–6 months of life [3]. However, the fetus accumulates iron mostly in the last trimester of pregnancy and preterm babies are at high risk of ID. Low-birth-weight (<2.5 kg) infants are also at increased
risk [see Lönnerdal and Hernell, this issue]. Children between 6 months and 3 years of age are particularly vulnerable to ID because they are rapidly growing and have an increased need for iron at a time when their iron stores from birth have become depleted. The prevalence of anaemia usually peaks around 18 months of age and adolescent girls are also at increased risk.

ID in children is usually due to low dietary intakes of iron and is likely to be worse in diets with high levels of substances that inhibit iron absorption such as calcium and phytates. Early introduction of undiluted cow’s milk can also cause ID. Thus, populations that eat little meat, fish or poultry and have high levels of cereals are most at risk. In addition, infection with intestinal helminths, especially hookworm, or heavy *Trichuris trichiura* infection may cause ID due to blood loss. Infection with *Schistosoma haematobium* also causes blood loss in the urine, and the prevalence and intensity increases in school-aged children and may cause ID.

Before discussing the possible effect of ID on children’s development, it is necessary to understand the basic processes of child development and the ecology of ID.

**Factors Affecting Child Development**

Children’s development is affected by a wide range of environmental conditions as well as genetics. There is now increasing evidence that brain structure and function can be affected by both the biological and psychosocial environment. Furthermore, the first 2–3 years are particularly sensitive to psychosocial and biological conditions, and the brain changes may have long-term effects. The timing and duration of experiences are important and affect long-term functioning. Risk factors tend to occur together and their effects on development can be cumulative or even interactive.

**Factors Associated with ID in Children**

ID is usually associated with a vast number of disadvantages that can themselves affect children’s development. In addition to prematurity, low birth weight and geohelminth infections, iron deficiency anaemia (IDA) is associated with numerous psychosocial disadvantages including low socio-economic status, poverty, poor quality of stimulation at home, lack of maternal warmth, low levels of maternal education and IQ, maternal depression, absent father [4] and minority groups [5]. It is clear that iron-deficient children may have poor development and different behaviour compared with non-deficient children for many reasons, and demonstrating an association between ID and child development cannot establish a causal relationship. Randomized controlled trials (RCTs) of iron supplementation treating or preventing IDA are needed to establish whether ID causes poor cognitive, motor and behavioural development.

**Effect of ID on Children’s Development**

We will first discuss whether there are biologically plausible mechanisms whereby ID could cause poor child development; then we will review studies of the effect of ID on children’s development.

**Mechanisms**

Hypothesized mechanisms whereby ID could affect children’s development include direct effects on brain structure and function and/or changes in children’s behaviour known as ‘functional isolation’ [6] leading to poor development.

**Brain Development**

There is ample evidence from animal research that ID causes changes to the brain structure and neurochemistry. Lozoff [7] recently summarized these changes, which are presented in the following. The formation of myelin is decreased. Myelin forms a fatty sheath around the axons and affects the speed of neural transmission. Altered cell metabolism [8] and morphology have also been recorded with decreases in dendritic growth and arborization and synapse formation. The changes are found especially in the hippocampus, which plays a major role in the development of memory. Changes in neurometabolites have also been found in the basal ganglia, which have an important role in higher cognitive functions and emotional processes and motor functions. Several neurotransmitters are also affected by ID including dopamine, serotonin, and norepinephrine. Some changes persist even after iron treatment. Behavioural changes have also been found in iron-deficient rats, which reflect the alterations in brain development. Changes in brain function have been demonstrated in infants with IDA using event-related potentials which measure transient changes in electrical activity of the
brain in response to stimuli. In one study, infants with IDA had delayed event-related potentials when performing attention and recognition memory tasks [9]. In other studies the central conduction time of auditory brain stem responses (response to auditory stimuli) were prolonged [10, 11]. In one study [11], the difference actually increased 12 months after iron treatment. The authors attributed prolonged central conduction time to impaired myelination, which has been observed in iron-deficient animals. Longer latencies in visual evoked potentials (response to visual stimuli) have also been found in 3- to 5-year-old children who had IDA in infancy [12]. In another study of 4-year-old children who had IDA in infancy [13] both their auditory brain stem responses and visual evoked potentials remained abnormal. However, the findings are not totally consistent and Sarici et al. [14] found no differences in auditory brain stem responses of iron-deficient infants compared to controls. Most studies with EEGs involved infants under 2 years of age, but recent studies in school-aged children show they also have abnormal EEGs associated with cognitive tasks, but they improve with iron treatment [15]. Therefore, it was suggested that, whereas older children’s EEGs improve with treatment, infants’ may not. Abnormal sleep patterns have been found in infants with IDA that is thought to reflect autonomic nervous system function [12, 16, 17]. In 2 RCTs, in Zanzibar and Nepal, sleep duration improved with iron + folic acid or iron + zinc supplementation, suggesting a causal link between micronutrients and sleep [18].

**Behaviour**

Another possible mechanism is functional isolation which was first described in undernourished rats [6]. These rats were shown to move around their environment less and explore less than better nourished animals. It was subsequently found that undernourished children behave in an analogous way [19]. Moreover, the mothers were also less stimulating in interactions with their undernourished children. It was thought that the mothers responded to their children’s altered behaviour by being less stimulating. Children acquire skills through exploration, therefore it was hypothesized that the behaviours of both child and mother contributed to their developmental delay. However, the timing of altered behaviour preceding the onset of developmental delay has not been established. Subsequently, many studies have shown that children with IDA behave in a similar way to undernourished children.

During developmental assessments, infants with IDA are more fearful, tense and withdrawn, less responsive and unhappier than non-anaemic children [4, 20–22]. They also make fewer attempts at test tasks, are less playful and have poorer attention than non-anaemic children [23].

Observational studies at home are less frequent. In situations where infants are free to play, those with IDA stay closer to their mothers, are more wary, hesitant, and easily tired and show less pleasure. At home, infants with IDA were more likely to be asleep, irritable, doing nothing, being carried, in bed, and less likely to be playing interactively with objects [23]. Many of these behaviours did not improve with iron treatment. Preschoolers with IDA also show similar types of behaviour. They display less social looking toward their mothers, and are slower to approach new toys and display positive affect compared with non-anaemic preschoolers [24]. Anaemic toddlers in Zanzibar were found to be less active at home [25], although in another study, their activity level varied by the context and was only reduced in the laboratory [26].

It is clear that there are several biologically plausible mechanisms whereby ID could cause changes to development and behaviour. However, it remains possible that these behaviours could be due to deprived environments associated with IDA rather than IDA itself.

Although not the main topic of this paper, ID in mothers may also affect child development. A recent study of maternal-child interaction in iron-deficient mothers showed that they were less sensitive to their 10-week-old children and their children were less responsive compared to iron-sufficient mothers with their children [27]. The mothers with IDA were randomized to iron treatment or placebo and when the children were 9 months of age, the iron-supplemented group was no longer different from a non-iron-deficient comparison group. Both latter groups were significantly better in several aspects of both mothers’ and children’s behaviour when interacting than the placebo iron-deficient group, whose maternal iron status remained low.

**Review of Studies**

There are a number of reviews on the effect of ID on children’s cognition and most concluded that IDA causes small deficits in cognition in school-aged children, although the effect on school achievement is not known and the effect on younger children remains con-
troversial [7, 28, 29]. The main reason for the lack of consensus about the effects on younger children is that most studies on the topic were observational or non-randomized trials. These are difficult to interpret because of the vast number of probable confounders. However, more recently, several RCTs have been conducted. This review of studies builds on previous reviews the first author was involved with [4] and a contribution to the report on iron and health for the Scientific Advisory Committee on Nutrition to the Food Standards Agency and Department of Health, UK, 2010. We have classified the studies by age of subjects (children under and over 3 years of age) and by study design including correlation, longitudinal, non-randomized treatment trials and RCTs and discuss randomized trials in most detail. We have selected the more important observational studies to discuss but included all RCTs we could find from searches of databases and discussions with experts in the field.

Cross-Sectional Observational Studies

Many cross-sectional studies have reported significant associations between haemoglobin (Hb) concentrations and measures of cognitive function and school achievement in older children and psychomotor development in younger children. Grantham-McGregor and Ani [4] identified 14 such studies, including correlational ones and studies often comparing anaemic with non-anaemic children as baseline measurements in treatment trials. Although many of these studies controlled for some socio-economic and nutritional variables, few had extensive controls. Additional studies include a large national survey of 6- to 16-year-olds (n = 5,398) in the USA [30] in which iron-deficient children with or without anaemia had significantly lower math scores than non-iron-deficient children after extensive adjustment for covariates (age, sex, race, poverty status, caretaker education and blood lead status). There was no association with 2 memory tests (digit span, block design) and a reading test. The prevalence of IDA was too small to examine relationships with IDA alone.

In a recent study, behavioural differences were related to ID in a dose-response way across 3 groups from iron-sufficient non-anaemic, to iron-deficient non-anaemic to IDA [31]. The behaviours showing a linear trend included shyness, orientation/engagement, soothability and positive affect. When an examiner attempted to engage the child in play, latency to engage (longer in IDA) and latency to move away from the examiner (shorter in IDA) also showed linear trends. These data suggest that effects of ID on behaviour could be apparent even before anaemia occurs and get worse with severity.

It is unknown why a small number of studies found no association with Hb concentration and cognitive function [32, 33]. These findings cause doubt as to the aetiology of the deficits.

Longitudinal Studies

Grantham-McGregor and Ani [4] identified 7 longitudinal studies of infants who had IDA or anaemia. A further longitudinal study has been reported but with a short follow-up [34]. The definition of anaemia and ID was often not clear. Four studies related Hb concentration as a continuous variable to cognitive development or school achievement. The remaining studies compared children with IDA or anaemia with non-anaemic children. The definition of anaemia varied.

Most importantly, all studies found that formerly anaemic children continued to be at a developmental disadvantage at follow-up. Most studies controlled for some social background variables, sex and birth weight, and some differences remained in every study but 1 [35]. In that study, the follow-up was short and early Hb levels were inconsistently related to IQ at different ages. Global measures of intelligence were generally used to assess cognition at follow-up. Two studies also looked at specific cognitive functions and the cognitive deficits found in the formerly anaemic children were not identical. Several studies found that formerly anaemic children had poorer educational outcomes and 2 reported that anaemic children had minor neurological dysfunction.

The Costa Rican study has the longest follow-up we are aware of and the children were reassessed at 11, 14 and 19 years of age [36, 37]. Formerly iron-deficient anaemic infants had persistent global cognitive deficits at 19 years of age (65% of initial sample) compared with those who were not iron deficient in infancy. There was a significant interaction between IDA and socio-economic status. In infants from lower socio-economic homes, those with IDA increased their cognitive deficit over time compared with iron-replete children from similar backgrounds. In contrast, infants from more affluent homes with IDA maintained the same level of deficits throughout the follow-up period. Detailed examination of cognitive functions showed executive function (inhibitory control, set-shifting, and planning) and memory deficits in the formerly anaemic children [37]. The authors suggested that these deficits may result from the long-term effects of early ID on the dopamine system and the hippocampus.
Discussion of Observational Studies

There is ample evidence of a concurrent association between IDA and poor development and behavioral differences both in infancy and older children. The longitudinal studies indicate that the association found in the first few years usually continue and may last up to adolescence, and 1 study suggests that it lasts at least to 19 years of age [36].

The level of anaemia at which effects on children's development are first apparent is difficult to determine. The definitions of anaemia varied in most studies from an Hb concentration between 61 and 95 g/l through below 105 g/l to below 110 g/l. In 1 study [34], the level of Hb at which motor development was found to decline was 95 g/l. However, in another study [31], behaviour was found to change in iron-deficient non-anaemic children.

The Costa Rican study [36] indicates that the size of the deficit is modified by socio-economic status. The final deficit attributed to IDA in infancy was as great as 1.67 SD scores (25 points) in poorer children compared with 0.6 SD (9 points) in more affluent ones. Most infants with IDA globally come from poor backgrounds and these findings raise concern that IDA in infancy may have sustainable and sizeable effects on cognition in these populations. As the infants with IDA were treated with iron in infancy, the findings also raise the question of whether the effects are remediable, as do the results of animal research on the effects on brain development discussed above. However, observational studies have to be interpreted with caution because of all the possible confounders. For example, stimulation in the home is rarely controlled for but has an important impact on young children's development.

Intervention Studies

It is possible to infer a causal link from iron supplementation studies. The most rigorous design is a preventive double-blind RCT, whereby healthy non-iron-deficient infants with a high risk of having IDA in the near future are randomized to treatment or placebo. This design is difficult and expensive to run because it needs very large samples; most importantly, if a large proportion of the placebo group do not develop ID, there may be insufficient statistical power. In contrast, interventions with only children with IDA are more efficient, needing smaller samples because all the children would be expected to benefit from iron supplementation. The main problem with these studies is that finding no benefit could mean that the initial deficits were not reversible.

Other requirements of an efficacy trial are that there must be some initial measure of iron status and evidence that the treatment was given with an increase in Hb or iron status compared with the placebo group. Also, the measure of child development used must be sensitive to the size of difference thought to be functionally relevant.

In what follows, we will first discuss treatment trials with children under 3 years of age divided into short- (<2 weeks) and longer-term treatment and finally discuss trials with children aged over 3 years.

Short-Term Randomized Trials with Children Aged under 3 Years

In several early studies in children under 3 years of age, iron supplementation was given for less than 2 weeks and there was no convincing evidence that psychomotor development was affected [4]. Therefore, we will not discuss short-term RCTs further. However, the efficacy of short-term iron treatment has not been well tested because it is very unlikely that the test used to assess the children's development (Bayley Scales) would change to any extent in such a short time. Different tests such as those measuring attention and tiredness might be more promising.

Non-Randomized Treatment Trials Lasting >2 Months with Children under 3 Years

We previously identified 4 treatment trials of iron supplementation with children who were iron deficient or had IDA that were not randomized but used non-anaemic iron-replete children as controls [21, 38–40]. We identified a further long-term trial from Turkey [41] which had 3 small groups of children: 37 with IDA, 40 non-iron-deficient (NAID) and 31 non-anaemic. Only the NAID group was randomized to treatment and the results from this group were not reported separately. Of the 5 trials, 3 did not catch up with the non-anaemic group [21, 39, 40], whereas the other 2 did catch up [38, 41]. In Turkey [41], the IDA groups began with poorer mental and motor development scores than the non-anaemic group, and the NAID group had poorer mental development than the non-anaemic group; after treatment, the non-anaemic, NAID and IDA groups were all similar.

Hasanbegovic and Sabanovic [42] found that children with an Hb concentration of less than 95 g/l had lower mental and motor development scores than children with an Hb level of 95–110 g/l and both groups had lower scores than a non-anaemic group. The deficit between the
2 anaemic groups increased after treatment with only children with an Hb level of 95–110 g/l showing some improvement. The authors suggested that children with Hb levels below 95 g/l had irreversible deficits.

In summary, it is difficult to explain why some samples of IDA children caught up with the non-anaemic groups with treatment and others did not. Neither severity of initial anaemia nor duration of treatment appears to explain the difference. Possible explanations are that socio-economic differences between the IDA and non-anaemic children varied across studies or that other micronutrient deficiencies were involved, such as zinc, in some populations that could affect the result. Treatment trials without a control group with similar levels of ID are unlikely to help determine causal relationships because children with IDA may develop at a different rate from iron-replete children. The longest follow-up study [36] suggests that IDA children from lower socio-economic status homes develop differently over time compared to iron-replete children from similar homes. Therefore, maintaining the same level of development could mask a treatment effect.

RCTs in Children Aged under 3 Years Lasting >2 Months

A systematic review [28] located 11 trials in infants and toddlers (<27 months). The authors concluded that there was no convincing evidence of a benefit on mental or motor development. Unfortunately, they included 4 short-term trials that are known not to be effective, leaving 7 RCTs with longer treatment. We located 14 randomized trials of iron treatment lasting more than 2 months [40, 43–55], although some of them had problems with the design, type of treatment or analyses. In the following section, we will discuss these trials grouped by the selection criteria of the sample: (a) children with IDA, (b) children with mixed levels of Hb and (c) preventive trials with non-anaemic infants. Assuming that iron treatment would only benefit iron-deficient children’s development, the size of the sample needed to demonstrate that significant differences increase from a to c. The studies are presented in table 1.

Children with IDA. We located only 3 double-blind RCTs with children with IDA (table 1a) [43, 48, 54]. We had difficulty classifying the trial in Zanzibar [54] because the age range was 12–48 months, motor milestones were assessed up to 36 months of age and language milestones up to 48 months. Also, although the children were not selected by Hb criteria, 97% were initially anaemic. The level of Hb may be misleading as malaria parasitaemia was highly prevalent. Iron supplementation for 12 months significantly improved language milestones in all children, whereas it only improved motor milestones in children with initial Hb concentrations below 90 mg/l. The milestones were assessed by mother’s report and the predictive validity of these measures is not well established. Idjradinata and Pollitt [48] reported a significant treatment effect on both mental and motor development in Indonesian children assessed using the Bayley Scales. However, the samples were very small. In contrast, Aukett et al. [43] did not find a significant treatment effect, although there was a suggestion of an effect in post hoc analyses. They assessed the children’s development with the Denver test, which is only a screening test and unlikely to be sensitive to small differences.

Children with Mixed Iron Status. We identified 3 double-blind RCTs which included children with mixed iron status (table 1b) [44, 49, 53]. In Indonesia [49], children were randomized to 4 groups receiving iron, zinc, iron + zinc or placebo. After 6 months of treatment, there was a significant interaction between iron and zinc on motor development. A small but significant benefit of iron was found on motor but not mental development, whereas iron + zinc or zinc alone showed no benefit. In Zanzibar [53], children were also randomized to 4 groups receiving iron + folate, zinc, iron + folate + zinc or placebo. The only outcome was a mother’s report of the age when the children started to walk unassisted collected every 2 weeks. The groups receiving iron + folate and iron + folate + zinc walked sooner than the untreated group. The effect was largest in children with IDA. The zinc treatment showed no effect, whereas it remains possible that folate had an effect.

In Bangladesh [44], children were randomized to 5 groups, each receiving different micronutrients including iron alone, zinc alone, iron + zinc, a mix of 16 multiple micronutrients or riboflavin which was used as a placebo. Motor scores on the Bayley Scales declined in all groups; however, the decreases were significantly smaller in infants who received iron and zinc together or multiple micronutrients. The group receiving only iron declined less than the riboflavin group, but the difference was not significant. It is unlikely that this study had sufficient statistical power to detect small differences.

Healthy, Non-Anaemic Children. Eight preventive RCTs with treatment lasting longer than 2 months were initially found (table 1c) [40, 45–47, 50–52, 55]. The children’s age ranged from 2 to 9 months and treatment lasted from 6 to 13 months.
### Table 1. Randomized trials in children ≤3 years of age, lasting ≥2 months

<table>
<thead>
<tr>
<th>Study; country</th>
<th>Sample</th>
<th>Study design</th>
<th>Measurements</th>
<th>Treatment effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aukett et al. [43], 1986; UK</td>
<td>Total (n = 110) aged 17–19 months (Treated (n = 54) Placebo (n = 56) All with Hb = 80–110 g/l (no other Fe cut-off))</td>
<td>DBRCT</td>
<td>Denver screening test, Anthropometry</td>
<td>No significant treatment effect on psychomotor skills. No difference between those with Hb increase &gt;20 g/l and those with less. Expected rate of development was achieved by 31% of iron-treated and 12% of the placebo group (p &lt; 0.05). Hb increased.</td>
</tr>
<tr>
<td>Idjradinata and Pollitt [48], 1993; Indonesia</td>
<td>Aged 12–18 months Total (n = 126)</td>
<td>DBRCT</td>
<td>Bayley Scales of infant development</td>
<td>Significant treatment effect in IDA groups in MDI and PDI. No longer any differences between treated IDA and NAID and Fe-replete groups. Fe-replete and ID groups had no significant treatment effect. Hb increased in IDA and ID group.</td>
</tr>
<tr>
<td>Stoltzfus et al. [54], 2001; Zanzibar</td>
<td>Aged 12–48 months 685 randomized, 538 completed study 417 aged 12–48 months had language assessment 293 aged 12–36 months had motor assessment 97%, Hb &lt;110 g/l 85%, malarial parasitaemia</td>
<td>DBRCT</td>
<td>Parental interview, Language milestones assessed in children 12–48 months and motor milestones assessed in those aged 12–36 months</td>
<td>Significant iron treatment effect on motor scores, only in children with baseline Hb &lt;90 g/l. Significant iron treatment effect on language scores across Hb range. No significant anthelmintic treatment effect on motor or language milestones. No treatment effect on Hb but significant effect on ferritin.</td>
</tr>
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### Table 1a. Longer-term randomized treatment trials in children aged ≤3 years with IDA or ID

<table>
<thead>
<tr>
<th>Study; country</th>
<th>Sample</th>
<th>Study design</th>
<th>Measurements</th>
<th>Treatment effects</th>
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<tr>
<td>Black et al. [44], 2004; Bangladesh</td>
<td>Total (n = 221) subsample from larger study aged 6 months 5 groups: (1) 20 mg Fe + 1 mg riboflavin (n = 49) (2) 20 mg zinc + 1 mg riboflavin (n = 49) (3) 20 mg Fe + 20 mg zinc + 1 mg riboflavin (n = 43) (4) Micronutrient mix (MM) (with 16 vitamins and minerals including 20 mg Fe, 20 mg zinc, 1 mg riboflavin) (n = 35) (5) 1 mg riboflavin (n = 45) All with Hb ≥90 g/l; approx. 68%, anaemic</td>
<td>DBRCT</td>
<td>Bayley Scales, HOME scale, Behaviour ratings: 3 factors, i.e. orientation-engagement, emotional regulation, motor quality</td>
<td>Significant group × time interaction for PDI and orientation. PDI scores decreased significantly less in the Fe + zinc and the MM groups compared to the riboflavin group. Fe group and zinc group n.s. MDI scores not affected by any treatment. Orientation decreased significantly less in the Fe and Fe + zinc groups than in the riboflavin group. No treatment effect on Hb concentration.</td>
</tr>
<tr>
<td>Lind et al. [49], 2004; Indonesia</td>
<td>Total (n = 680) aged 6 months Each group (n = 170) 4 treatment groups: (1) Fe (10 mg/day), (2) zinc (10 mg/day) (3) Fe (10 mg/day) + zinc (10 mg/day) (4) placebo All with Hb &gt;90 g/l, 41% anaemic</td>
<td>DBRCT</td>
<td>Bayley Scales, Behaviour ratings</td>
<td>Significant interaction between Fe and zinc treatment for PDI. Significant iron effect on PDI (p = 0.042). No other group significant. No effect of Fe + zinc combined on PDI. No treatment effect on MDI or behaviour.</td>
</tr>
<tr>
<td>Olney et al. [53], 2006; Zanzibar</td>
<td>n = 404 aged 5–11 months n = 103: Fe 12.5 mg + folate (FeFA) n = 87: zinc 10 mg n = 101: FeFA + zinc n = 114: placebo 65% anaemic</td>
<td>DBRCT</td>
<td>Age of walking By interview every 2 weeks</td>
<td>Treatment: Fe (± zinc) had a significant effect on age of walking; improvement greatest in children with initial IDA. Zinc not significant.</td>
</tr>
</tbody>
</table>
Four RCTs could not be interpreted because of design problems and are not included in the table [40, 45, 47, 52]. In a Canadian trial [45], there was no difference between the treatment and placebo groups in Hb concentration after treatment, therefore it would not be expected to find child development differences. The presence of malaria confused the results in the study by Heywood et al. [47], and analysis was not reported by ‘intention to treat’ in another study [40]. In an English RCT [52], no benefits of treatment were found; however, there were...
insufficient measures of initial and final Hb levels. It was therefore impossible to assess whether there was any difference between the groups in iron status at the end.

Two of the 4 remaining RCTs [50, 55] also had design problems. An English trial was not double blind [55]; one group was given fortified formula until 18 months of age, while the other group was given money to buy cow’s milk. Benefits were found in the fortified formula group considering developmental quotients on the Griffiths Test 6 months after the treatment stopped. It is possible that other constituents in the formula could have been responsible for the observed benefits, or cows’ milk could have reduced the absorption of other nutrients.

In Chile [50], the original assignment to a formula with high and low levels of iron resulted in no differences in iron status of the children, so treatment had to be changed over half way through the study. Children were then assigned to a high-iron formula or cow’s milk with multivitamins without iron. High iron supplementation had no effect on the mental and motor scores on the Bayley Scales, or a test of recognition memory, but there were improvements in speed of information processing, behaviour, and age of crawling/creeping. However, with supplementation procedures changing half way through and cow’s milk being given to some in the control group, we should be cautious about inferring that iron treatment caused these differences.

The remaining 2 RCTs were double-blind RCTs. In Canada [51], children were randomized to a high and low iron-fortified formula from 2 months until 15 months of age. The high iron group had significantly higher motor scores on the Bayley Scales than the placebo group at 9 and 12 months of age; however, benefits were no longer significant at 15 months. There was no benefit to mental development. However, the difference between the groups in iron status was particularly small at 15 months.

Friel et al. [46] reported that iron-replete infants supplemented at 1 month of age for 5 months had significantly higher motor scores in the Bayley Scales than the placebo group at 9 and 12 months of age; however, benefits were no longer significant at 15 months. There was no benefit to mental development. However, the difference between the groups in iron status was particularly small at 15 months.

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A further recent study [56] was not included with previous reviews involving very low-birth-weight infants (<1,301 g) who were randomized to early (mean 14 days) or late (mean 61 days) iron supplementation. The early supplemented children had slightly (but not significant-ly) better neurological, cognitive, school achievement and disability outcomes at 5 years of age.

Summary of and Comment on Supplementation Trials with Children Aged ≤3 Years

There is no clear evidence that short-term iron treatment is beneficial to psychomotor and mental development of anaemic children aged 3 years or under; however, this has not been rigorously tested. Longer-term iron treatment trials that were not randomized are difficult to interpret because of differences in the development of non-anaemic and anaemic children who are usually from poorer social backgrounds.

We summarize only studies that are double-blind RCTs with evidence of subjects in treated groups having higher levels of Hb or iron status than the placebo group at the end or some time during treatment so that they can be interpreted with confidence. There were 3 randomized longer trials with anaemic children and 2 showed benefits in motor and mental or language development [48, 54]. Of the 3 randomized trials of children with mixed iron status, 2 studies reported significant benefits for motor development only [49, 53]. The third reported beneficial effects on motor development from iron and zinc combined but only a non-significant benefit from iron alone [44]. Two of 2 preventive trials [46, 51] reported beneficial effects on motor but not mental development.

There is sufficient evidence from the above to indicate that motor development is affected by iron status. Of the 7 studies that looked at mental/language development, only 2 [48, 54] found benefits for mental or language development, which is insufficient to come to conclusions. However, the 5 remaining studies had limited power owing to relatively small samples or including non-anaemic children or having small difference in Hb levels after treatment, so this remains to be tested. Also, it may take longer for mental development to respond to nutritional improvement. In studies of energy and protein supplementation with undernourished children in this age range, motor development usually showed benefits before mental development. There is also the possibility suggested by longitudinal observational studies and animal research that early ID may have irreversible effects on mental development.

Few studies contained high-risk children such as those with low birth weight or undernutrition and they need investigating because effects may differ.
<table>
<thead>
<tr>
<th>Study and country</th>
<th>Sample</th>
<th>Study design and treatment</th>
<th>Measures</th>
<th>Treatment effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soemantri et al. [62], 1985; Central Java</td>
<td>IDA (n = 78) Fe replete (n = 41)</td>
<td>DBRCT Treatment: 10 mg/kg ferrous sulphate/day Placebo = tapioca and saccharin; Duration = 3 months</td>
<td>Baseline: Raven Progressive Matrices (IQ), Pre- and post-treatment: Abbreviated standard achievement test Bourden-Wisconsin test for concentration</td>
<td>Fe-treated IDA group improved significantly more in concentration and in school achievement than placebo IDA group. No significant difference between Fe-treated and placebo NA groups. Post-treatment score of NA group still significantly better than Fe-treated IDA group. Change in Hb: Treated IDA = 26.7 g/l; placebo IDA = –11.7 g/l. Treated NA = 7.6 g/l; placebo NA = 6.7 g/l.</td>
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<tr>
<td>Soewondo et al. [63], 1989; Indonesia</td>
<td>IDA (n = 49) Fe depleted (n = 57) Fe replete (n = 70)</td>
<td>DBRCT All groups received Fe or placebo Treatment = 50 mg Fe/day in syrup or placebo; Duration = 8 weeks</td>
<td>Peabody Picture Vocabulary test (PPVT) Two discrimination learning tasks Four oddity tasks</td>
<td>PPVT no treatment effect. Discrimination learning tasks remained too difficult; discrimination learning: treated IDA group learned significantly faster than treated Fe-replete group (p &lt; 0.05). Oddity task: no effect in trials 1 and 2; in trials 3 and 4, interaction between Fe treatment and group; Fe-treated IDA group had significantly higher scores than Fe-treated Fe-replete group and Fe-replete placebo group had higher scores than the IDA placebo group. Hb change in Fe-treated IDA = 9 g/l; placebo IDA = 1 g/l.</td>
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<tr>
<td>Pollitt et al. [60], 1989; Thailand</td>
<td>IDA (n = 101) aged 9–11 years in 16 schools Fe depleted (n = 47) Fe replete (n = 127)</td>
<td>DBRCT All dewormed on enrolment and after 3 months Randomized to Fe or placebo before Fe status known, then divided into groups by iron status Treatment: 50 mg ferrous sulphate/day for 2 weeks, then 100 mg/day for 14 weeks Duration = 16 weeks</td>
<td>Raven Progressive Matrices Thai language and maths test Controlled for school and grade</td>
<td>No treatment effect on school subjects. Hb: IDA placebo and treated groups increased in Hb by 14 and 20 g/l, respectively; Fe-depleted placebo and treated groups increased by 1 and 5 g/l, respectively; both Fe-replete placebo and Fe-treated decreased by 2 g/l.</td>
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<td>Seshadri and Gopaldas [61] (study 2), 1989; India</td>
<td>n = 28 aged 5–6 years (14 pairs of boys matched for IDA, height, weight, Hb, IQ, per capita income, and mother’s educational level) IDA: Hb &lt;105 g/l</td>
<td>DBRCT Each pair randomized to iron or placebo Both groups dewormed Treatment = 40 mg Fe + 0.2 mg folic acid/day Placebo = sugar Duration = 60 days</td>
<td>Draw a man IQ WISC</td>
<td>Both groups improved significantly in WISC. Fe-treated group significantly better than controls in verbal and performance tasks at end. Mean change in Hb = +24 g/l in treated group and –8 g/l in controls.</td>
</tr>
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<td>Seshadri and Gopaldas [61](study 3), 1989; India</td>
<td>n = 48 boys from one school aged 8–15 years (16 groups of 3, each matched for age, Hb level, and scores in cognitive function tests) IDA: Hb &lt;105 g/l NA: Hb &gt;115 g/l</td>
<td>DBRCT Each matched triplet randomized into 3 groups: (1) Treatment = 30 mg Fe/day (2) Treatment = 40 mg Fe/day (3) Placebo = brown sugar Duration = 60 days</td>
<td>Visual recall Digit span Maze (visual motor coordination) Clerical task</td>
<td>Both Fe treatment groups significantly improved in all cognitive tests except for the maze test in the 30 mg group, no change in the placebo group Compared with placebo, the 30 mg group had significantly higher scores in the clerical task and visual recall tests, and the 40 mg group had significantly higher scores in all 4 tests. IDA placebo boys showed no significant improvements; the 40 and 30 mg iron-treated IDA group significantly improved in several tests NA showed no improvements</td>
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<tr>
<td>Seshadri and Gopaldas [61](study 4), 1989; India</td>
<td>Girls from 4 schools aged 8–15 years 83 pairs matched for age, and Hb 63 pairs finished study</td>
<td>DBRCT Matched pairs randomized to: (1) Treatment = 60 mg Fe/day (2) Placebo = sugar tablets Duration = 60 days</td>
<td>Visual recall Digit span Maze Clerical task</td>
<td>Fe-treated IDA children significantly better than placebo IDA children in overall scores and in clerical tasks, and mazes Fe-treated NA group improved significantly only in mazes</td>
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<td>Bruner et al. [57], 1996; USA</td>
<td>NA Fe-deficient girls (n = 81) aged 13–18 years Treated (n = 40) Placebo (n = 41) IDA: Hb &lt;120 g/l for white and 115 g/l for black girls Fe deficient: normal Hb + ferritin &lt;12 μg/l</td>
<td>DBRCT Treatment = 260 mg Fe/day Duration = 8 weeks</td>
<td>Brief Test of Attention (BTA) Symbol Digits Modalities Test (SDMT) Visual Search and Attention (VSAT) Hopkins Verbal Learning Test (HVLT)</td>
<td>No significant effect on BTA, SDMT or VSAT HVLT: iron-treated group improved significantly more in score of 3 free recall items than the placebo group (p &lt; 0.02) No significant difference in delayed recall or recognition parts of test Hb and serum ferritin higher for Fe-treated group</td>
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<tr>
<td>Metallinos-Katsaras et al. [64], 2004; Greece</td>
<td>IDA (n = 21) Fe replete (n = 28) Aged 3–4 years in day care centers IDA: Hb &lt;112 g/l and TS &lt;16% SF &lt;12 μg/l or Hb increase &gt;10 g/l after Fe supplementation Fe replete: Hb &gt;120 g/l and either TS &gt;20% or SF &gt;12 μg/l</td>
<td>DBRCT Both groups randomized to treatment or placebo Treatment: 15 mg/day Fe and multivitamins Placebo (multivitamins only) Duration = 2 months Post hoc reclassification of iron group using Hb change</td>
<td>Computerized tests: Simple Reaction Time (SRT) Test; Continuous Performance Task (CPT); 3 Oddity Learning (OL) Tasks</td>
<td>SRT: no treatment effect in IDA or Fe-replete children CPT: Fe-treated IDA children made significantly fewer errors of commission (p &lt; 0.05) and showed higher accuracy (p &lt; 0.05) and were significantly more efficient (p &lt; 0.05) than placebo IDA group Significant interaction between group and treatment on speed of response: iron-treated iron-replete group was slower than placebo iron-replete children, whereas treated IDA was faster than placebo IDA OL: no treatment effect</td>
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</table>

DBRCT = Double-blind randomized controlled trial; EP = erythrocyte protoporphyrin; Fe = iron; NA = non-anaemic; SF = serum ferritin; TS = transferrin; WISC = Wechsler Intelligence Scale for Children.
RCTs in Children Aged 3 Years and Over

The meta-analysis by Sachdev et al. [28] with 6 trials in older children found evidence of a benefit in cognitive tests from iron treatment. We previously found 14 treatment trials in older children [4]. If we exclude studies in which the method of assignment to treatment was not randomization, a placebo was not used and statistics were not reported, that leaves 10 randomized trials of iron treatment in children aged over 3 years with IDA or ID [32, 57–63]. One study was only reported in a letter [59] and there were insufficient details to evaluate. In another study [32], all IDA children were treated with iron, but the NAID group was alternately assigned to iron treatment or placebo. However, the iron status of both treated and placebo NAID groups returned to normal by the end of the study, so differences in development would not be expected. In another study, the method of precise assignment to treatment was not reported [58], furthermore, very few children were anaemic (2.9%) or had low ferritin levels (16.9%), so the effect of iron was not adequately tested.

Details of the remaining 8 studies are given in table 2 including a more recent study with a few children under 3 years [64]. They were all double-blind RCTs [57, 60–64].

Six of the 8 double-blind RCTs used cognitive tests as outcome measures. Seshadri and Gopaldas [61] found that in study 2, the iron-treated group had significantly higher IQs than the control group after treatment. However, children were given folic acid with iron, which may have had an independent benefit. In study 3 and 4 [61], the treated groups had significantly better scores in several cognitive tests than the placebo group at the end. One study found significant improvements with iron treatment in IDA children in speed of processing [64] and another study with NAID girls observed beneficial effects on memory [57] but not on 3 other cognitive tests. No significant treatment effects were reported in another trial [63].

Only 2 studies examined school achievement [60, 62]. An Indonesian study [62] showed a significant improvement, whereas a study in Thailand [60] did not.

Summary of and Comment on Supplementation Trials with Children Aged ≥3 Years

Five of 6 double-blind RCTs of iron supplementation that used cognitive tests for outcome measures reported some benefits. Unfortunately, several studies did not control for initial levels of cognitive function and only reported postintervention differences. There are insufficient data to determine whether NAID children also benefit, but the only study found small benefits.

One of 2 double-blind RCTs assessing school achievement [60, 62] found benefits. A possible explanation for the lack of improvement in Thailand [60] is that the Hb cut-off value for IDA was higher than in Indonesia [62]. Also, Hb levels of the placebo group in Thailand improved probably due to deworming so that the difference in iron status at the end was very small. The quality of schooling is also likely to have played a role.

Threshold Levels

Several studies show that effects are greater the more severe the ID in a dose-response way [31, 42, 53] and a meta-analysis also suggested that IDA children were more likely to benefit from iron supplementation [28]. There is insufficient evidence to determine the level of ID at which children’s function is first affected. Some improvements with iron treatment were found in non-anaemic iron-deficient girls [57].

Implications of Findings

If iron supplementation had no potentially adverse effects, then universal supplementation or fortification would be the obvious recommendation. However, in iron-replete children, there is inconsistent evidence of a detrimental effect of giving iron on certain morbidities (diarrhoea and malaria) and on growth. Therefore, the benefits of supplementation have to be weighed against any potential harm. This varies in different populations and has been discussed in other papers. It is clear that children should be treated for ID and prevented from getting it. General improvements to children’s diets and prompt treatment of infections would be a first step to prevention.

Overall Summary

Although there is considerable research on the effect of ID on child development, there are relatively few double-blind RCTs of iron supplementation with adequate power.

There is considerable evidence showing that:
(1) there is altered electrical activity in the brain in response to certain stimuli in children with IDA;
(2) children with IDA usually have poor cognitive and motor development and behavioural differences that
are sustained through adolescence. However, ID is associated with a large number of psychosocial and economic disadvantages, which could account for some or all of the children’s functional deficits;

(3) iron supplementation usually has beneficial effects on motor development in children with IDA under 3 years of age;

(4) iron supplementation has beneficial effects on cognition in iron-deficient anaemic school-aged children;

(5) the effects of ID increase with severity.

However, more evidence is needed to show:

– the effect of IDA on mental development of children under 3 years of age;
– if school achievement benefits from iron supplementation in children with IDA;
– if the effects of IDA are worse in poorer children;
– if ID in mothers affects their behaviour which in turn affects children’s development;
– what is the threshold at which ID affects function;
– what are the effects of IDA on high-risk children such as those with low birth weight or undernutrition;
– what are the effects of iron supplementation in iron-replete children on development and health.

**Key Messages**

- Children with IDA are at risk of poor concurrent and future motor and mental development and behavioural differences.
- Children with IDA generally come from poor socio-economic backgrounds, which could account for some or all of their deficits.
- Children with IDA have changes to evoked potentials in the brain.
- Iron supplementation usually shows beneficial effects on motor development in children with IDA aged under 3 years but the effect on mental development is not clear.
- Iron supplementation shows beneficial effects on cognitive function in children aged over 3 years with ID.

**References**


