Iron deficiency and child development

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Abstract

Iron deficiency is widespread in infants and young children, especially in developing countries. Animal models provide convincing evidence that, despite iron repletion, iron deficiency during the brain growth spurt alters metabolism and neurotransmission, myelination, and gene and protein profiles. In the human, there is compelling evidence that 6- to 24-month-old infants with iron-deficiency anemia are at risk for poorer cognitive, motor, social–emotional, and neurophysiologic development in the short- and long-term outcome. In contrast to inconsistent developmental effects of iron therapy for iron-deficient infants, recent large, randomized trials of iron supplementation in developing countries uniformly show benefits of iron, especially on motor development and social–emotional behavior. These results indicate that adverse effects can be prevented and/or reversed with iron earlier in development or before iron deficiency becomes severe or chronic. New findings also point to the need for more attention to the developmental effects of prenatal iron deficiency.

Key words: Anemia, brain, development, early childhood, infancy, iron deficiency

Introduction

The prevalence of anemia among children less than 4 years of age is estimated to range between 46% and 66% in developing countries, and half of the anemia is thought to be iron-deficiency anemia [1]. The peak period is 6 to 24 months. Poor, minority, and/or immigrant infants and toddlers in developed countries are also at increased risk for iron deficiency, with or without anemia [2]. Thus, the effects of iron deficiency on child development could have a major societal impact in regions where iron deficiency is widespread and adverse impacts on individual infants and young children everywhere. This background paper begins with a brief summary of current basic science understanding of iron deficiency and the developing brain, drawing on studies in animal (rodent) models. The paper then turns to research on iron deficiency in infants and toddlers—the period of peak prevalence. Sections summarize alterations during the period of deficiency, effects of iron therapy, long-term outcome, and results of randomized, controlled supplementation trials. Finally, the paper considers recent research on prenatal iron deficiency in human neonates and new nonhuman primate models. Issues of timing, duration, and severity are emphasized throughout.

Iron deficiency and the developing brain: Evidence from rodent models

Many developing central nervous system (CNS) processes are highly dependent on iron-containing enzymes and proteins. Thus, iron deficiency might have multiple and varied effects, particularly during the brain growth spurt. A conceptual framework for such brain and behavior effects is shown in **figure 1** [3]. CNS processes and behavioral domains are shown as overlapping ovals to emphasize their interconnections during development. Altered gene and protein profiles may regulate the affected CNS processes, and changes in physiologic regulatory processes (neuroendocrine, autonomic, and sleep-wake cycle) may affect all the behaviors. Brain and behavior are shown as having reciprocal effects, as do altered behavior and environmental experience.

By experimental induction of iron deficiency and control over environmental conditions, animal models

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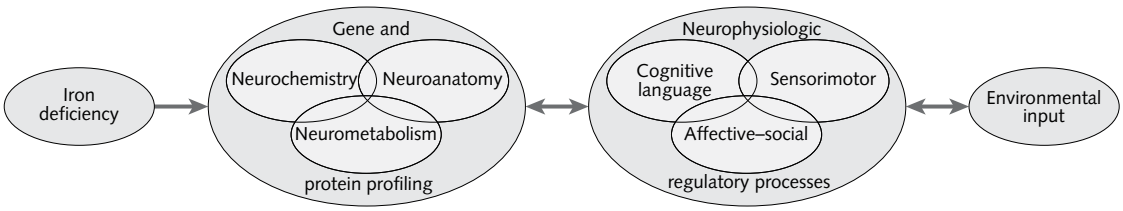

FIG. 1. Conceptual framework for brain and behavior effects of early iron deficiency
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help establish a causal role for iron deficiency in altering brain and behavior. Environmental control is an important consideration, since environmental disadvantage often co-occurs with human iron deficiency, making causal inferences problematic in the human [4, 5]. Animal models also help identify underlying CNS mechanisms and differing effects of iron deficiency at different stages of brain development. The first rodent studies of developmental iron deficiency induced iron deficiency predominantly at weaning [6, 7]. This stage in rat development would be roughly toward the end of the brain growth spurt in the human. To be more comparable to the iron deficiency commonly observed in the human infant, recent rodent models focus on the maternal–fetal unit, inducing iron deficiency in earlier periods of brain development. This approach has allowed more assessment of brain–behavior effects based on the timing, severity, and duration of early iron deficiency.

Gestation/lactation rodent models are relevant to the common worldwide human condition, in which mothers have iron deficiency during pregnancy and children are iron deficient in the infant/toddler period. Initial applications of this model produced severe iron-deficiency anemia that was accompanied by growth restriction [8]. A recent modification makes the model closer to dietary iron deficiency in human infants, with more moderate brain iron deficiency and minimal effect on growth [9, 10]. Another model focuses on fetal and neonatal iron deficiency to help understand human conditions with severe fetal brain iron deficiency but adequate dietary iron after birth (e.g., intrauterine growth restriction and gestational diabetes mellitus) [11, 12].

Early rodent studies showed overall reductions in brain iron concentration, despite postnatal iron repletion [6, 8, 13]. Even with earlier iron repletion in gestation and/or lactation rat models with severe iron deficiency [14], there are whole-brain and regional iron deficits that persist to adulthood despite treatment [6, 8, 11, 15–18]. However, in the new model of more moderate brain iron deficiency, lower brain iron was corrected in all but one region [9]. Nonetheless, brain–behavior differences persisted (see below).

Early iron deficiency directly affects oligodendrocytes, which form myelin, the fatty acid sheath around axons that helps speed neural transmission [19]. Some myelin lipids and proteins are reduced into adulthood, despite iron repletion, affecting myelin content and compaction [20] (also see reviews [14, 21]). Both myelinogenesis and iron uptake are at their peak during the early postnatal period. Hypomyelination could impact function in many systems.

Early iron deficiency also alters brain cell metabolism and morphology. This has been best studied in the hippocampal formation, especially in the fetal/neonatal rodent model. There are decreases in neuronal metabolism, dendritic growth and arborization, and synapse formation [11, 22–25]. Again, changes persist past puberty despite iron repletion at weaning. The hippocampus is involved in recognition memory and other important cognitive and emotional functions through a variety of networks. In the gestation/lactation rodent model that avoids marked growth restriction [9, 10], pronounced changes in striatal neurometabolites were recently observed [26]. The striatum is part of the basal ganglia; striatal networks relate to higher-order cognitive and emotional processes (executive functions), motivated behavior, positive affect, and reward-related processing (see review [27]), as well as motor functioning. Thus, striatal alterations, like hippocampal ones, are likely to have many manifestations, given their role in widely distributed networks.

New studies also show short- and long-term iron-deficiency effects on gene and protein profiles [28–30]. From over 300 genes that differed in iron-deficient animals at weaning, 12 were selected for verification by real-time polymerase chain reaction; 6 were up-regulated on microarray studies and 6 were down-regulated [29]. In contrast, all five genes that differed in adulthood were down-regulated; these genes affect cytoskeletal stability and synaptic function and thus could have broad effects.

The earliest studies of iron deficiency in the rat implicated the dopamine neurotransmitter system in the basal ganglia, especially the D_2 receptor (see reviews [7, 14]). More recent studies show that transporters for dopamine, serotonin, and norepinephrine, dopamine levels, and D_1 receptors are also affected (see reviews [14, 21], also [31–37]). Such changes were observed

even before reduced brain iron was detectable in the new, more moderate iron-deficiency model [10]. Iron repletion to adulthood did not correct all the changes [9]. Early iron deficiency also reduces the neuronal surface protein Thy1 [30, 38].

Behavioral alterations in iron-deficient rats are consistent with the CNS effects [39] (see reviews [7, 14, 21]). During development, a number of sensorimotor reflexes are delayed [10]. Forelimb placing tasks and grooming sequences—both dependent on striatal dopamine—are also delayed or disrupted, with alterations persisting into adulthood [9]. Other persistent consequences that are observed when iron deficiency occurs during gestation and lactation include less exploration, more hesitancy, and poorer spatial learning (thought to reflect hippocampal dysfunction) [8, 9, 39, 40].

The inability of iron repletion beginning at weaning to reverse changes in the brain in gestation/lactation rodent models points to the importance of earlier intervention for iron deficiency. A limited number of studies examined iron repletion around the rat equivalent of human birth. They also show long-lasting brain–behavior differences in rodent models with severe iron deficiency [16, 23, 25, 41], but the effects in the more moderate brain iron-deficiency model are unknown. However, studies with iron repletion even earlier, corresponding to the third trimester in the human, suggest complete correction of regional and total brain iron [42, 43] and neurotransmitter function [42], but not dendritic organization in the hippocampus [43]. These studies indicate that the ability of iron repletion to correct brain iron deficits and some brain–behavior effects depends on timing.

Developmental alterations in infants with iron-deficiency anemia

Global outcomes

Most human research has focused on children under 2 years of age because of the peak prevalence in this period. Despite a recent increase in research (see reviews [3, 44–46]), studies often differ in design, infant age, or measures. Fifteen studies, conducted in countries around the world, assessed overall functioning in otherwise healthy full-term infants in the 6- to 24-month age range [47–62]. By design, children with prematurity, malnutrition, illness, etc., were excluded. Poorer cognitive, motor, and/or social–emotional functioning was observed while infants were iron-deficient in all but one study. Standardized cognitive development test scores of iron-deficient anemic infants averaged 6 to 15 points lower than infants with better iron status (effect sizes, 0.5 to 1.3 SD) [53–58, 62]. Language was also affected [48, 53, 54, 63]. Among 12 studies that included a standardized assessment of motor development [48, 50, 51, 53–59, 61, 62], 9 observed that infants with iron-deficiency anemia received lower motor test scores, averaging 9 to 15 points lower (effect sizes, 0.7 to 1.1 SD) [48, 50, 53–55, 57–59, 62]. Furthermore, a population study in the UK found that a hemoglobin level less than 95 g/L at 8 months predicted poorer locomotor development at 18 months [64]. Virtually every study that examined social–emotional behavior found differences in iron-deficient anemic infants (e.g., more wary, hesitant, solemn, unhappy, closer to their mothers, less social interaction, etc.) [49, 50, 65–69]. Recent studies of infants at risk for stunting also reported poorer pretreatment motor development in those with iron-deficiency anemia [70, 71].

Neurophysiologic and neurocognitive outcomes

Though consistently observed, global outcomes give little indication about the specific CNS processes affected by iron-deficiency anemia in infancy. Only a few studies have assessed neurophysiologic functioning. Compared with nonanemic infants, those with iron-deficiency anemia show slower neural transmission (using auditory brainstem responses) [72, 73], altered rapid eye movement density in active sleep [74], poorer recognition memory with ERPs (event-related potentials) [75], and altered electroencephalographic frontal asymmetry [76]. Spontaneous motor activity, assessed actigraphically, showed differences between home and laboratory [77, 78], suggesting that iron-deficient anemic infants respond differently to context — with reduced motor activity associated with the stress or unfamiliarity of the laboratory [77, 78]. Only one neurophysiology study did not find differences [79].

Duration, severity, and timing

Issues of the duration, severity, and timing of iron deficiency have received little systematic study in infant studies, partly because separating them is difficult; i.e., infants who become iron-deficient earlier are also more likely to be so longer and more severely. The only direct data about duration in the human infant come from a small early study in Chile [54]. The few infants with iron-deficiency anemia at both 9 and 12 months had lower cognitive and motor scores at 12 months than those with iron-deficiency anemia at 12 months only. Other evidence is indirect. In an early small study of 6- to 24-month-olds in Guatemala [47], cognitive score differences were markedly lower only among the oldest infants [48]. Long-lasting differences in a Costa Rica cohort [80, 81], up to young adulthood (see below [82, 83]), may also relate to chronicity, since infants were identified at 12 to 23 months and are likely to have been iron deficient for some time [53]. Only a few infant studies have assessed severity. One early study reported

lower global cognitive test scores and behavioral differences in nonanemic iron-deficient infants [49], but two others did not observe lower scores unless iron deficiency was severe enough to produce anemia [53, 54]. Other studies reported poorer outcome only with even more severe iron deficiency [47, 63]. For instance, in a Zanzibar study of young children (6 to 59 months) at high risk for malnutrition, motor benefits of iron supplementation were observed only in those with initial hemoglobin levels less than 90 g/L, but language benefits were observed regardless of hemoglobin level [63]. However, a recent study shows that effects of iron deficiency even without anemia can be detected with more sensitive brain–behavior measures: there were linear effects of iron status on specific neurocognitive, motor, social–emotional, and sensory system outcomes [60, 76, 84]. With regard to timing, poorer outcome has been observed with iron-deficiency anemia in every age period assessed to date. Although the study designs and samples do not permit identification of differential effects depending on timing, effects of iron deficiency are likely to differ based on the time course of brain and behavioral development. Differing response to iron therapy seems to indicate that this is the case.

Effects of iron therapy

Many of the above studies included assessments before and immediately after iron therapy. Early reports of improvement after 7 to 10 days [49, 85] have not been replicated. Of studies with a full course of iron treatment (3 to 6 months), seven used standardized tests and are sufficiently similar for comparison [53–59]. In four of them, lower developmental test scores persisted in iron-deficient anemic infants after treatment [53, 54, 56, 58], whereas they improved in three studies [55, 57, 59]. Although the reasons for the differing results have not been identified, pretreatment scores were much lower in iron-deficient anemic infants in the studies that showed improvement than in studies that did not. With respect to neurophysiologic outcomes, a study in Chile found differences in auditory system transmission, activity, and sleep state organization, even after a full year of iron treatment [72, 74, 77, 78]. Thus, the majority of studies find that developmental deficits are not corrected with iron therapy in infancy.

In contrast, the few available studies of older preschoolers (2 to 6 years) consistently show improvements with iron treatment. Although again differing in design, measures, and/or child age, studies in India, Greece, the United States, Guatemala, and Indonesia generally show poorer performance in those with iron-deficiency anemia, with differences in activity and cognitive function that improve with iron therapy [86–90]. Several of these studies had strong designs (randomized, placebo-controlled trials). Studies of school-aged children, adolescents, and adults also indicate cognitive and work performance effects of iron deficiency, with or without anemia, that generally improve following iron therapy (reviewed in [14, 44]) [91]. Thus, it appears that treatment for iron deficiency occurring after infancy is generally effective in reversing behavioral effects. Findings of persisting differences with iron-deficiency anemia in infancy suggest that iron deficiency may have different and/or less reversible effects when it occurs during the brain growth spurt.

Long-term outcome

Global outcomes

Nine studies—from Costa Rica, Israel, France, the United States, and Yugoslavia—assessed overall developmental outcomes years after iron-deficiency anemia in infancy. There have been five follow-ups at preschool age (< 6 years) [92–96], three at school age (6 to 10 years) [97–99], and one in adolescence [81, 83]. Although the studies varied with respect to the detail in which iron status was determined and the results reported, all show long-term effects. Children who had iron-deficiency anemia, anemia presumably due to iron deficiency, or other evidence of chronic, severe iron deficiency in infancy do worse on tests of overall mental, motor, and social–emotional functioning, despite iron therapy. A recent meta-analysis estimated the long-term effects on IQ to be a decrease of 1.73 points for each 10 g/L decrease in hemoglobin [1].

One of these studies was population based, including all children born in an entire county in Florida in the targeted time period [98]. Anemia in infancy, based on hemoglobin screening in the WIC (Women, Infant, and Children) program, was associated with special education placement at 10 years, based on the criteria used by the Florida Department of Education for mild or moderate mental retardation. Although this study was limited in that hemoglobin was the sole measure of iron status, it is exceptional in relating anemia in infancy (presumably due to iron deficiency) to increased risk of mental retardation or special education placement among school-aged children in an entire population (N = 3,771). After a basic set of background characteristics was controlled for, the risk of placement in special education increased by 1.28 for each unit lower in hemoglobin at entry into the WIC program.

The sole follow-up into adolescence, of Costa Rican children born at term and free of health problems other than iron deficiency, showed twice as much grade repetition by 11 to 14 years and more anxiety/depression, social problems, and inattention reported by both parents and teachers [81]. Longitudinal analyses (hierarchical linear modeling), controlled for background

factors, showed no catch-up in motor scores through early adolescence (last time of motor assessment) [100] and a widening gap for cognitive scores through 19 years of age [83]. The widening gap in cognitive scores was particularly marked for formerly iron-deficient children from families of lower socioeconomic status: the difference increased from 10 points in infancy to 25 points in young adulthood (**fig. 2**) [83].

Neurocognitive and neurophysiologic outcomes

More brain-based long-term outcomes are available only for the follow-up studies in Costa Rica and Chile. Both used the brain–behavior framework shown in **figure 1**. In the follow-up at 4 years in Chile, formerly iron-deficient anemic children showed longer latencies on auditory and visual evoked potentials than children who were nonanemic in infancy [101]. The magnitude of the effects was large—1 to 1.2 SD. The findings indicate long-lasting alterations in neurotransmission in two sensory systems that are essential for learning from the physical and social environment. Both the auditory and the visual systems are rapidly myelinating in infancy, and long-lasting differences in sensory evoked potentials are consistent with the persisting myelin deficits that have been documented in rodent models of early iron deficiency. Overnight polysomnographic recordings showed many sleep-wake cycle differences between formerly iron-deficient anemic and nonanemic children [102]. These findings indicate that iron-deficiency anemia can alter key components of the internal temporal order within the 24-hour cycle.

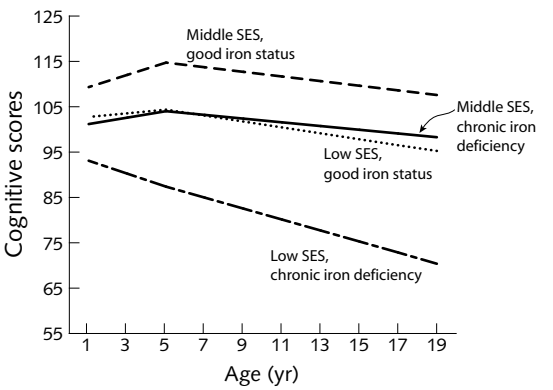

FIG. 2. Cognitive composite scores over time, comparing infant iron status groups within middle and low socioeconomic status (SES) families in Costa Rica. Iron status group and SES level each affected initial scores (p values < .01). Change over time differed only for the chronic-iron-deficiency group in low-SES families ($p < .05$). Each participant is represented once: good iron status ($N = 67$) compared with chronic iron deficiency ($N = 20$) in middle-SES families and good iron status ($N = 65$) compared with chronic iron deficiency ($N = 33$) in low-SES families. Symbols are placed at the average age for each assessment
Source: Reprinted with permission from Lozoff et al. [83].

In both Chile and Costa Rica, children with iron-deficiency anemia or other indications of chronic, severe iron deficiency in infancy had poorer performance on tests of some specific cognitive functions. For the Costa Rica sample at 11 to 14 years, poorer performance was observed for tachistoscopic threshold, spatial memory, and selective attention [81]. At 5 and 10 years in the Chile follow-up and 19 years in the Costa Rica follow-up, formerly iron-deficient children did worse on executive function tasks, particularly those that require inhibition and planning [82, 103]. These tasks involve prefrontal-striatal networks where dopamine is the primary neurotransmitter. There were also long-lasting alterations in response patterns of prolactin (basal prolactin is regulated by dopamine), suggesting long-lasting effects on pituitary dopamine function and/or stress responses [104].

Thus, studies from countries around the world have yielded generally consistent results regarding long-term outcome. On average, children who had iron-deficiency anemia, chronic severe iron deficiency, or anemia presumably due to iron deficiency in infancy continue to perform less well than peers who had good iron status in infancy. As a group, they do worse on tests of overall cognitive, motor, and social–emotional functioning and on specific neurocognitive tests at preschool age, at school age, and during adolescence. Neurophysiological differences are observed through the preschool period, and the 10-year follow-up of the Chile sample suggests that differences still persist. Iron deficiency typically occurs in disadvantaged environments, but the findings from the several follow-up studies have been statistically significant after control for background factors in a wide variety of settings.

Randomized, controlled trials of iron supplementation in human infants

A comprehensive 2001 review of studies on the behavioral and developmental effects of iron deficiency [44] and a 2003 Cochrane review [105] concurred that the association between iron-deficiency anemia in infancy and poorer behavioral and developmental outcomes was strong, but that causal connections needed to be proven by further randomized, controlled trials. Since then, new randomized supplementation trials have further supported a causal role for lack of iron in poorer behavioral and developmental outcomes in the first 2 years of life. In contrast to studies of therapeutic iron for iron-deficiency anemia, supplementation trials in populations at risk for iron deficiency—with random assignment to supplemental iron or placebo regardless of initial iron status—show quite consistent benefits, especially in the motor and social–emotional

domains. There are 11 such studies, 5 involving healthy full-term infants [106–110] and 6 involving infants at risk for stunting and numerous infectious diseases [63, 111–115]. The design of these studies is the most powerful way to address the issue that iron deficiency typically goes together with environmental disadvantage in humans. Randomized, controlled trials thus provide the strongest basis for causal inferences in human studies. Smaller effect sizes are meaningful in supplementation trials, relative to effect sizes in studies of iron-deficient or iron-deficient and anemic infants, given the unselected nature of the samples.

Among preventive trials with healthy full-term infants in the 6- to 24-month range, only a large study in Chile (N = 1,657) showed benefits of iron supplementation on cognitive functioning [107]. Infants who received supplemental iron between 6 and 12 months had shorter looking times on a visual recognition memory task, suggesting better high-speed information processing on a measure that predicts later IQ. Regarding motor function, a preventive trial in Canada showed higher motor scores at 9 and/or 12 months in the group that received prophylactic iron [106], and the Chile study found that infants who received iron crawled somewhat earlier and more were rated as less tremulous [107]. Two of the three trials that assessed the affective domain in healthy term infants reported differences as well. Infants who received prophylactic iron received better personal/social scores in a British study [108]. In the Chile study, more of the group that received supplemental iron showed positive affect, interacted socially, checked their mother's response, could be soothed by words or objects, and protested when interesting toys were taken away [107]. This study is noteworthy in that infants had iron-deficiency anemia for only a short time: with blood testing before and after the supplementation period, iron-deficiency anemia could not have lasted more than 6 months. A small randomized, controlled trial involving breastfed infants in Canada showed a benefit of even earlier iron supplementation. Infants who received iron between 1 and 6 months had better grating visual acuity and motor scores at 12 months than those receiving placebo [110].

In addition to the Chile study, there are five other large, recent supplementation trials in developing countries. They involved infants at risk for stunting and infectious diseases in Zanzibar, Indonesia, Bangladesh, and India [63, 112–115], often assessing iron with or without other micronutrients. Sample sizes ranged from around 220 to 440 in Bangladesh and India to 350 to 650 in Zanzibar and Indonesia. All supplementation trials in developing countries showed benefits of iron for motor development, and three of four that assessed the social–emotional domain showed benefits as well [107, 113, 114]. The magnitude of effects at the conclusion of the trials ranged from 0.27 to 0.39 SD for motor outcomes and 0.30 to 0.41 SD for social–emotional ones [46]. (A small earlier study in Papua New Guinea suggested an effect of iron on fixation time, a cognitive outcome, but only in infants without malarial parasitemia [111].) No long-term follow-ups have been reported.

There is also one randomized, controlled trial of food iron fortification that included a developmental outcome [116]. In a sample of over 250 South African infants, those randomly assigned to receive micronutrient-fortified maize-meal porridge between 6 and 12 months improved in motor development more than infants assigned to receive unfortified porridge. The effect size for improved motor outcome, based on parental report of gross motor milestones, was 0.34 SD, very similar to that observed with iron supplements.

Several of the above supplementation trials were not included in a recent meta-analysis [45] and might have changed the finding of no effect of iron in infancy if the meta-analysis had included them and separated supplementation from treatment trials. These new supplementation trials provide increasing evidence that lack of iron causes poorer behavior and development in infants. The trials also suggest that effects can be prevented and/or reversed with iron interventions before iron deficiency becomes chronic and severe [46].

Prenatal iron deficiency

Maternal iron status during pregnancy was unknown in the studies of infants and toddlers described above. It is thus unclear whether the observed effects are due to iron deficiency postnatally or both pre- and postnatally. Recent research strongly suggests that fetal and neonatal iron deficiency adversely affects developing brain–behavior systems. During fetal development, iron is prioritized to red cells at the expense of other tissues, including the brain [117]. When iron supply does not meet iron demand, the brain is at risk even though the infant may not be anemic. The most common etiology of reduced iron supply to the fetus is maternal iron deficiency. Overall, 56% of pregnant women in developing countries are anemic, with half of cases attributed to iron deficiency [118, 119]. Previous thinking that infants are protected from maternal iron deficiency is no longer accepted [120, 121]. A number of studies have shown that iron-deficiency anemia during pregnancy, especially if severe, constitutes a significant threat to fetal iron stores (see review [120]), placing both the fetal and the neonatal brain at risk. Neonates born to such mothers have lower mean ferritin concentrations (reflecting fetal iron storage pools) and may have iron-deficiency anemia if the mother is severely anemic [120, 122]. In preanemic iron-deficient pregnant women, low ferritin concentrations also correlate with lower cord serum ferritin concentrations [123]. Thus, infants born with a low ferritin concen-

tration appear to have a reduced fetal iron endowment and are therefore at risk for earlier onset of postnatal iron deficiency that can affect brain development.

Perinatal iron deficiency is beginning to receive more attention in human developmental studies. In the sole study of premature infants, a variety of reflexes were less mature in those with iron-deficiency anemia [124]. Two studies related perinatal iron deficiency to newborn temperament-like behaviors in full-term infants. One reported higher levels of irritability in infants of mothers with iron-deficiency anemia [125]. In the other, poorer iron status at birth (cord blood ferritin and hemoglobin) correlated with higher levels of negative emotionality and lower levels of alertness and soothability [126]. Another study found that infants of mothers with iron-deficiency anemia in the peripartum period had lower scores for hand-eye movement at 10 weeks and locomotion at 9 months [127]. A longitudinal study found that lower cord ferritin levels predicted poorer behavior and development at 5 years, specifically, poorer auditory comprehension of language, fine motor skills, and tractability (indexing self-regulation) [96]. In addition, maternal anemia in pregnancy accounted statistically for 14% of mental retardation in black children in the US Collaborative Perinatal Project, which involved over 35,700 children followed from the prenatal period to 7 years [128].

Some groups of newborns are at risk for iron deficiency because of increased fetal iron demand, rather than maternal iron deficiency [117]. The most common reason for increased demand is chronic fetal hypoxia that results in increased iron utilization for compensatory red cell production. This commonly occurs with intrauterine growth restriction (IUGR) and maternal diabetes mellitus (gestational or pregestational). IUGR complicates up to 30% of pregnancies worldwide and approximately 5% of pregnancies in the United States [117]. In developing countries, maternal undernutrition is the most common contributing factor, whereas in developed countries, maternal hypertension is the leading cause. Glucose intolerance is found in 5% to 10% of pregnancies in the United States [117]. In both conditions, neonatal brain iron concentration is reduced by 33% to 40% on autopsy [129, 130]. Cord serum ferritin concentrations are below the 5th percentile in 50% of live-born IUGR newborns [123]. Cord serum ferritin concentrations are abnormal in up to 65% of live-born infants of diabetic mothers, with 25% having values low enough (< 35 μg/L) to suggest prenatal brain iron deficiency [117, 131].

Considerable research documents that both IUGR infants and those born to diabetic mothers are developmentally at risk in the short and long term [132–134]. Research on their brain function is much more limited. Hippocampal integrity has been assessed in infants of diabetic mothers by neuroimaging using event-related potentials (ERPs). In keeping with effects of prenatal iron deficiency on the hippocampus in rodent models, infants of diabetic mothers had poorer recognition memory, as measured by ERPs and/or behavioral tests as newborns and at 8 and 12 to 36 months [135–137]. The effects were mostly in those infants with low cord ferritin levels [136, 137].

Nonhuman primate models

New nonhuman primate models also point to the importance of prenatal iron deficiency. One established a model of purely prenatal versus purely postnatal iron deprivation in infant rhesus monkeys, experimentally induced by diet [138, 139]. Even without producing iron-deficiency anemia and despite an iron-sufficient diet postnatally, prenatal iron deprivation led to a behavioral syndrome of increased impulsivity and a decrease in the usual caution and/or withdrawal in novel situations. This pattern contrasted with postnatal iron deprivation, again without iron-deficiency anemia, which led to a behavioral syndrome more like that in iron-deficient anemic human infants and toddlers (e.g., hyperemotionality and tenseness) and cognitive delay. Since none of the monkeys had iron-deficiency anemia at any time, this study is also relevant to the issue of severity. It shows that iron deficiency without anemia—pre- or postnatally—can affect behavior in nonhuman primate infants.

Monkey models also show that prenatal iron status strongly influences postnatal iron status. In the monkey model described above, lack of supplemental iron postnatally did not produce iron deficiency or iron-deficiency anemia in infants with adequate prenatal iron nutrition [138, 139]. Another study, also in rhesus monkeys, assessed the iron status of infants born to monkey mothers that were either iron deficient or iron sufficient at conception, with half of each group provided with an iron-fortified diet throughout pregnancy. Infant iron status was related to maternal preconception iron status, regardless of diet condition during pregnancy [140]. These results again draw attention to the importance of maternal iron status, potentially even before conception. There is a single related human study, which points to the same conclusion [141].

Summary and conclusions

Rodent models with experimental designs provide convincing evidence that early iron-deficiency anemia alters metabolism and neurotransmission in major brain structures, such as the basal ganglia and hippocampus, and disrupts one brain-wide process—myelination. New research also shows altered gene and protein profiles [30]. For all these systems, differences are found before and after iron repletion when iron

deficiency is induced during gestation and/or lactation (brain growth spurt).

In the human, there is compelling evidence that 6- to 24-month-old infants with iron-deficiency anemia are at risk for poorer cognitive, motor, social–emotional, and neurophysiological development in the short term. Iron-deficiency anemia in this age period is also consistently associated with poorer long-term outcome. Iron therapy in infancy does not consistently improve developmental outcome. However, iron therapy for iron deficiency occurring after infancy typically reverses the observed effects. In contrast to inconsistent effects of iron therapy in iron-deficient anemic infants, recent large, randomized trials of iron supplementation in developing countries uniformly show benefits of iron, especially on motor development and social–emotional behavior. These results indicate that adverse effects can be prevented and/or reversed with iron earlier in development or before iron deficiency becomes severe or chronic. The issue of optimal timing of intervention also pertains to prenatal iron deficiency. Poorer developmental outcome, especially neurocognitive and social–emotional, has been shown in recent studies of fetal/neonatal iron deficiency in human and nonhuman primate infants.

Taken together, the results emphasize the importance of protecting the developing brain from iron deficiency. Evidence has steadily accumulated that postnatal iron supplementation can reduce iron deficiency and iron-deficiency anemia and improve developmental outcome. New findings point to the need for more attention to the developmental effects of prenatal iron deficiency, especially given the high worldwide prevalence rates of both iron deficiency in pregnancy and IUGR and the increasing rates of diabetes in pregnancy with the global epidemic of obesity. Nonhuman primate models suggest that preventing fetal and neonatal iron deficiency by maternal iron supplementation can further protect developing brain and behavior systems.

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References

1. Stoltzfus RJ, Mullany L, Black RE. Iron deficiency anaemia. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, eds. Comparative quantification of health risks: Global and regional burden of disease attribution to selected major risk factors. Vol 1. Geneva: World Health Organization, 2004:163–209.
2. Brotanek JM, Halterman J, Auinger P, Flores G, Weitzman M. Iron deficiency, prolonged bottle-feeding, and racial/ethnic disparities in young children. Arch Pediatr Adolesc Med 2005;159:1038–42.
3. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol 2006;13:158–65.
4. Lozoff B. Has iron deficiency been shown to cause altered behavior in infants? In: Dobbing J, ed. Brain, behaviour, and iron in the infant diet. New York: Springer-Verlag, 1990:107–31.
5. Pollitt E. Developmental sequel from early nutritional deficiencies: Conclusive and probability judgements. J Nutr 2000;130:350S–3S.
6. Dallman PR, Siimes M, Manies EC. Brain iron: Persistent deficiency following short-term iron deprivation in the young rat. Br J Haematol 1975;31:209–15.
7. Youdim MB. Nutrient deprivation and brain function: Iron. Nutrition 2000;16:504–8.
8. Felt BT, Lozoff B. Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early development. J Nutr 1996;126:693–701.
9. Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR, Georgieff MK, Lozoff B. Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. Behav Brain Res 2006;171:261–70.
10. Beard JL, Felt B, Schallert T, Burhans M, Connor JR, Georgieff MK. Moderate iron deficiency in infancy: Biology and behavior in young rats. Behav Brain Res 2006;170:224–32.
11. DeUngria M, Rao R, Wobken JD, Luciana M, Nelson CA, Georgieff MK. Perinatal iron deficiency decreases cytochrome c oxidase (CytOx) activity in selected regions of neonatal rat brain. Pediatr Res 2000;48:169–76.
12. Rao R, DeUngria M, Sullivan D, Wu P, Wobken JD, Nelson CA, Georgieff MK. Perinatal brain iron deficiency increases the vulnerability of rat hippocampus to hypoxic ischemic insult. J Nutr 1999;129:199–206.
13. Dallman PR, Spirito RA. Brain iron in the rat: Extremely slow turnover in normal rats may explain long-lasting effects of early iron deficiency. J Nutr 1977;107:1075–81.
14. Beard JL, Connor JR. Iron status and neural functioning. Annu Rev Nutr 2003;23:41–58.
15. Findlay E, Ng KT, Reid RL, Armstrong SM. The effect of iron deficiency during development on passive avoidance learning in the adult rat. Physiol Behav 1981; 27:1089–96.
16. Weinberg J, Levine S, Dallman PR. Long-term consequences of early iron deficiency in the rat. Pharmacol Biochem Behav 1979;11:631–8.
17. Chen Q, Connor JR, Beard JL. Brain iron, transferrin and ferritin concentrations are altered in developing iron-deficient rats. J Nutr 1995;125:1529–35.
18. Erikson K, Pinero DJ, Connor JR, Beard JL. Regional brain iron, ferritin and transferrin concentrations during iron deficiency and iron repletion in developing rats. J Nutr 1997;127:2030–8.
19. Connor JR, Menzies SL. Relationship of iron to oligo-

dendrocytes and myelination. Glia 1996;17:83–93.
20. Ortiz E, Pasquini JM, Thompson K, Felt B , Butkus G, Beard J, Connor JR. Effect of manipulation of iron storage, transport, or availability on myelin composition and brain iron content in three different animal models. J Neurosci Res 2004;77:681–9.
21. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64(5 pt 2):S34–43.
22. Pokorny J, Yamamoto T. Postnatal ontogenesis of hippocampal CA1 area in rats. II. Development of ultrastructure in stratum lacunosum and moleculare. Brain Res Bull 1981;7:121–30.
23. Jorgenson LA, Wobken JD, Georgieff MK. Perinatal iron deficiency alters apical dendritic growth in hippocampal CA1 pyramidal neurons. Dev Neurosci 2003;25:412–20.
24. Rihn LL, Claiborne BJ. Dendritic growth and regression in rat dentate granule cells during late postnatal development. Dev Res Dev Brain Res 1990;54:115–24.
25. Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK. Perinatal iron deficiency alters the neurochemical profile of the developing rat hippocampus. J Nutr 2003;133:3215–21.
26. Ward K, Tkac I, Jing Y, Felt B, Beard J, Connor J, Schallert T, Georgieff MK, Rao R. Gestational and lactational iron deficiency alters the developing striatal metabolome and associated behaviors in young rats. J Nutr 2007;137:1043–9.
27. Dahl RE. Adolescent brain development: A period of vulnerabilities and opportunities. Keynote address. Ann NY Acad Sci 2004;1021:1–22.
28. Siddappa AJ, Rao R, Wobken JD, Casperson K, Leibold EA, Connor J, Georgieff MK. Iron deficiency alters iron regulatory protein and iron transport protein expression in the perinatal rat brain. Pediatr Res 2003;53:800–7.
29. Clardy SL, Wang X, Zhao W, Liu W, Chase GA, Beard JL, Felt BT, Connor JR. Acute and chronic effects of developmental iron deficiency on mRNA expression patterns in the brain. J Neural Transm Suppl 2006;(71):173–96.
30. Wang X, Wiesinger J, Beard J, Felt B, Menzies S, Earley C, Allen R, Connor J. Thy1 expression in the brain is affected by iron and is decreased in Restless Legs Syndrome. J Neurol Sci 2004;220:59–66.
31. Erikson K, Jones B, Beard JL. Iron deficiency alters dopamine transporter functioning in rat striatum. J Nutr 2000;130:2831–7.
32. Beard JL, Erikson KM, Jones BC. Neonatal iron deficiency results in irreversible changes in dopamine function in rats. J Nutr 2003;133:1174–9.
33. Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. Pharmacol Biochem Behav 2001;69:409–18.
34. Chen Q, Beard JL, Jones BC. Abnormal rat brain monoamine metabolism in iron deficiency anemia. J Nutr Biochem 1995;6:486–93.
35. Beard JL, Chen Q, Connor JR, Jones BC. Altered monoamine metabolism in caudate-putamen of iron deficient rats. Pharmacol Biochem Behav 1994;48:621–4.
36. Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, Beard JL. Iron deficiency: Differential effects on monoamine transporters. Nutr Neurosci 2005;8:31–8.
37. Nelson C, Erikson K, Piñero DJ, Beard JL. In vivo dopamine metabolism is altered in iron-deficient anemic rats. J Nutr 1997;127:2282–8.
38. Ye Z, Connor JR. Identification of iron responsive genes by screening cDNA libraries from suppression subtractive hybridization with antisense probes from three iron conditions. Nucleic Acids Res 2000;28:1802–7.
39. Beard JL, Erikson KM, Jones BC. Neurobehavioral analysis of developmental iron deficiency in rats. Behav Brain Res 2002;134:517–24.
40. Piñero D, Jones B, Beard JL. Variations in dietary iron alter behavior in developing rats. J Nutr 2001;131:311–8.
41. Ben-Shachar D, Ashkenazi R, Youdim MB. Long-term consequence of early iron-deficiency on dopaminergic neurotransmission in rats. Int J Dev Neurosci 1986;4:81–8.
42. Unger EL, Paul T, Murray-Kolb LE, Felt B, Jones BC, Beard JL. Early iron deficiency alters sensorimotor development and brain monoamines in rats. J Nutr 2007;137:118–24.
43. Jorgenson L, Sun M, O'Connor M, Georgieff MK. Fetal iron deficiency disrupts the maturation of synaptic efficacy in area CA1 of the developing rat hippocampus. Hippocampus 2005;15:1094–102.
44. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001;131(2S-2):649S–68S.
45. Sachdev H, Gera T, Nestel P. Effect of iron supplementation on mental and motor development in children: Systematic review of randomised controlled trials. Public Health Nutr 2005;8:117–32.
46. Walker SP, Wachs TD, Gardner JM, Lozoff B, Wasserman GA, Pollitt E, Carter JA; International Child Development Steering Group. Child development: Risk factors for adverse outcomes in developing countries. Lancet 2007;369:145–57.
47. Lozoff B, Brittenham GM, Viteri FE, Wolf AW, Urrutia JJ. The effects of short-term oral iron therapy on developmental deficits in iron-deficient anemic infants. J Pediatr 1982;100:351–7.
48. Lozoff B, Brittenham GM, Viteri FE, Wolf AW, Urrutia JJ. Developmental deficits in iron deficient infants: Effects of age and severity of iron lack. J Pediatr 1982;101:948–52.
49. Oski FA, Honig AS, Helu B, Howanitz P. Effect of iron therapy on behavior performance in nonanemic, iron-deficient infants. Pediatrics 1983;71:877–80.
50. Walter T, Kovalskys J, Stekel A. Effect of mild iron deficiency on infant mental development scores. J Pediatr 1983;102:519–22.
51. Johnson DL, McGowan TJ. Anemia and infant behavior. Nutr Behav 1983;1:185–92.
52. Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. Arch Dis Child 1986;61:849–57.
53. Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, Jimenez R, Mora LA, Gomez I, Krauskopf D. Iron deficiency anemia and iron therapy: Effects on infant developmental test performance. Pediatrics 1987;79:981–95.
54. Walter T, De Andraca I, Chadud P, Perales CG. Iron deficiency anemia: Adverse effects on infant psychomotor development. Pediatrics 1989;84:7–17.

55. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. Lancet 1993;341:1–4.
56. Lozoff B, Wolf AW, Jimenez E. Iron-deficiency anemia and infant development: Effects of extended oral iron therapy. J Pediatr 1996;129:382–9.
57. Akman M, Cebeci D, Okur V, Angin H, Abah O, Akman AC. The effects of iron deficiency on infants' developmental test performance. Acta Paediatr 2004;93:1391–6.
58. Hasanbegovic E, Sabanovic S. Effects of iron therapy on motor and mental development of infants and small children suffering from iron deficiency anaemia. Med Arh 2004;58:227–9. (in Bosnian)
59. Antunes H. Iron deficiency anaemia in infants—A prospective neurodevelopment evaluation. Porto, Portugal: Faculty of Medicine, University of Portugal, 2004.
60. Shafir Liberzon T, Angulo-Barroso R, Calatroni A, Angelilli ML, Jacobson SW, Lozoff B. Iron deficiency affects motor development in 9-month-old infants. Pediatr Res 2005;57:1731.
61. Driva A, Kafatos A, Salman M. Iron deficiency and the cognitive and psychomotor development of children: A pilot study with institutionalized children. Early Child Dev Care 1985;22:73–82.
62. Hokama T, Gushi KM, Nosoko N. Iron deficiency anaemia and child development. Asia Pac J Public Health 2005;17:19–21.
63. Stoltzfus RJ, Kvalsvig JD, Chwaya HM, Montresor A, Albonico M, Tielsch JM, Savioli L, Pollitt E. Effects of iron supplementation and anthelmintic treatment on motor and language development of preschool children in Zanzibar: Double blind, placebo controlled study. BMJ 2001;323:1389–93.
64. Sherriff A, Emond A, Bell JC, Golding J, ALSPAC Study Team. Should infants be screened for anaemia? A prospective study investigating the relation between haemoglobin at 8, 12, and 18 months and development at 18 months. Arch Dis Child 2001;84:480–5.
65. Lozoff B, Klein NK, Prabucki KM. Iron-deficient anemic infants at play. J Dev Behav Pediatr 1986;7:152–8.
66. Deinard AS, List A, Lindgren B, Hunt JV, Chang PN. Cognitive deficits in iron-deficient and iron-deficient anemic children. J Pediatr 1986;108(5 pt 1):681–9.
67. Lozoff B, Wolf AW, Urrutia JJ, Viteri FE. Abnormal behavior and low developmental test scores in iron-deficient anemic infants. J Dev Behav Pediatr 1985;6:69–75.
68. Lozoff B, Klein NK, Nelson EC, McClish DK, Manuel M, Chacon ME. Behavior of infants with iron-deficiency anemia. Child Dev 1998;69:24–36.
69. Honig AS, Oski FA. Solemnity: A clinical risk index for iron deficient infants. Early Child Dev Care 1984;16:69–84.
70. Kariger PK, Stoltzfus RJ, Olney D, Sazawal S, Black R, Tielsch JM, Frongillo EA, Khalfan SS, Pollitt E. Iron deficiency and physical growth predict attainment of walking but not crawling in poorly nourished Zanzibari infants. J Nutr 2005;135:814–9.
71. Siegel EH, Stoltzfus RJ, Kariger PK, Katz J, Khatry SK, LeClerq SC, Pollitt E, Tielsch JM. Growth indices, anemia, and diet independently predict motor milestone acquistion of infants in south central Nepal. J Nutr 2005;135:2840–4.
72. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: Delayed maturation of auditory brain stem responses. Am J Clin Nutr 1998;68:683–90.
73. Li YY, Wang HM, Wang WG. The effect of iron deficiency anemia on the auditory brainstem response in infant. Zhonghua Yi Xue Za Zhi 1994;74:367–9, 392. (in Chinese)
74. Algarin C, Peirano P, Garrido M, Lozoff B. Iron deficient anemic infants have decreased rapid eye movements density in active sleep [abstract]. Sleep 2003;(suppl):A146.
75. Burden MJ, Westerlund AJ, Armony-Sivan R, Nelson CA, Jacobson SW, Lozoff B, Angelilli ML, Jacobson JL. An event-related potential study of attention and recognition memory in infants with iron deficiency anemia. Pediatrics 2007;120:e336–45.
76. Abrams JM, Jacobson SW, Lozoff B, Nelson CA. EEG correlates of iron deficiency in infancy. Pediatr Res 2005;57:1287.
77. Angulo-Kinzler RM, Peirano P, Lin E, Algarin C, Garrido M, Lozoff B. Twenty-four-hour motor activity in human infants with and without iron deficiency anemia. Early Hum Dev 2002;70:85–101.
78. Angulo-Kinzler RM, Peirano P, Lin E, Garrido M, Lozoff B. Spontaneous motor activity in human infants with iron-deficiency anemia. Early Hum Dev 2002;66:67–79.
79. Sarici SU, Serdar MA, Dundaroz MR, Unay B, Akin R, Deda G, Gokcay E. Brainstem auditory-evoked potentials in iron-deficiency anemia. Pediatr Neurol 2001;24:205–8.
80. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991;325:687–94.
81. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000;105:E51.
82. Burden M, Koss M, Lozoff B. Neurocognitive differences in 19-year-olds treated for iron deficiency in infancy. Pediatr Res 2004;55:279A
83. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency and low socioeconomic status: A longitudinal analysis of cognitive test scores to 19 years. Arch Pediatr Adolesc Med 2006;160:1108–13.
84. Oski FA, Honig AS. The effects of therapy on the developmental scores of iron-deficient infants. J Pediatr 1978;92:21–5.
85. Metallinos-Katsaras E, Valassi-Adam E, Dewey KG, Lönnerdal B, Stamoulakatou A, Pollitt E. Effect of iron supplementation on cognition in Greek preschoolers. Eur J Clin Nutr 2004;58:1532–42.
86. Pollitt E, Leibel RL, Greenfield DB. Iron deficiency and cognitive test performance in preschool children. Nutr Behav 1983;1:137–46.
87. Seshadri S, Gopaldas T. Impact of iron supplementation on cognitive functions in preschool and school-aged children: The Indian experience. Am J Clin Nutr 1989;50(3 suppl):675–86.
88. Pollitt E, Saco-Pollitt C, Leibel RL, Viteri FE. Iron deficiency and behavioral development in infants and preschool children. Am J Clin Nutr 1986;43:555–65.
89. Soewondo S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool

children: Bandung, Indonesia. Am J Clin Nutr 1989;50(3 suppl):667–74.
90. Li R, Chen X, Yan H, Deurenberg P, Garby L, Hautvast JG. Functional consequences of iron supplementation in iron-deficient female cotton workers in Beijing, China. Am J Clin Nutr 1994;59:908–13.
91. Palti H, Pevsner B, Adler B. Does anemia in infancy affect achievement on developmental and intelligence tests? Hum Biol 1983;55:183–94.
92. Dommergues JP, Archambeaud MP, Ducot B, Gerval Y, Hiard C, Rossignol C, Tchernia G. Iron deficiency and psychomotor development scores: A longitudinal study between 10 months and 4 years of age. Arch Fr Pediatr 1989;46:487–90. (in French)
93. De Andraca I, Walter T, Castillo M, Pino P, Rivera P, Cobo C. Iron deficiency anemia and its effects upon psychological development at preschool age: a longitudinal study. Nestle Foundation Nutrition Annual Report (1990). Vevey, Switzerland: Nestec, 1991:53–62.
94. Wasserman GA, Graziano JH, Factor-Litvak P, Popovac D, Morina N, Musabegovic A, Vrenezi N, Capuni-Paracka S, Lekic V, Preteni-Redjepi E, Hadzialjevic S, Slavkovich V, Kline J, Shrout P, Stein Z. Consequences of lead exposure and iron supplementation on childhood development at age 4 years. Neurotoxicol Teratol 1994;16:233–40.
95. Tamura T, Goldenberg RL, Hou J, Johnston KE, Cliver SP, Ramey SL, Nelson KG. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. J Pediatr 2002;140:165–70.
96. Palti H, Meijer A, Adler B. Learning achievement and behavior at school of anemic and non-anemic infants. Early Hum Dev 1985;10:217–23.
97. Hurtado EK, Claussen AH, Scott KG. Early childhood anemia and mild or moderate mental retardation. Am J Clin Nutr 1999;69:115–9.
98. Cantwell RJ. The long term neurological sequelae of anemia in infancy. Pediatr Res 1974;342:68.
99. Shafir T, Angulo-Barroso R, Calatroni A, Jimenez E, Lozoff B. Effects of iron deficiency in infancy on patterns of motor development over time. Hum Mov Sci 2006;25:821–38.
100. Algarin C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: Long-lasting effects on auditory and visual system functioning. Pediatr Res 2003;53:217–23.
101. Peirano PD, Algarin CR, Figueroa M, Garrido MI, Lozoff B. Nocturnal sleep consolidation is still affected at age 10-year in healthy children who presented iron deficiency anemia in infancy. J Sleep Res 2006;15(suppl 1):227.
102. Peirano P, Algarin C, Garrido M, Nunez JC, Angulo-Barroso R, Lozoff B. Cerebral executive function in preadolescents is affected by iron deficiency in infancy. Pediatr Res 2004;55:279A.
103. Felt B, Jimenez E, Smith J, Calatroni A , Kaciroti N, Wheatcroft G, Lozoff B. Iron deficiency in infancy predicts altered serum prolactin response 10 years later. Pediatr Res 2006;60:513–7.
104. Logan S, Martins S, Gilbert R. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. Cochrane Database Syst Rev 2001;(2): CD001444.
105. Moffatt ME, Longstaffe S, Besant J, Dureski C. Prevention of iron deficiency and psychomotor decline in high-risk infants through use of iron-fortified infant formula: A randomized clinical trial. J Pediatr 1994;125:527–34.
106. Lozoff B, De Andraca I, Castillo M, Smith JB, Walter T, Pino P. Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants. Pediatrics 2003;112:846–54.
107. Williams J, Wolff A, Daly A, MacDonald A, Aukett A, Booth IW. Iron supplemented formula milk related to reduction in psychomotor decline in infants for inner city areas: Randomised study. BMJ 1999;318:693–7.
108. Morley R, Abbott R, Fairweather-Tait S, MacFayden U, Stephenson T, Lucas A. Iron fortified follow on formula from 9 to 18 months improves iron status but not development or growth: A randomised trial. Arch Dis Child 1999;81:247–52.
109. Friel JK, Aziz K, Andrews WL, Harding SV, Courage ML, Adams RJ. A double-masked, randomized control trial of iron supplementation in early infancy in healthy full-term breast-fed infants. J Pediatr 2003;143:582–6.
110. Heywood A, Oppenheimer S, Heywood P, Jolley D. Behavioral effects of iron supplementation in infants in Madang, Papua New Guinea. Am J Clin Nutr 1989;50(3 suppl):630–40.
111. Lind T, Lönnerdal B, Stenlund H, Gamayanti IL, Ismail D, Seswandhana R, Persson LA. A community-based randomized controlled trial of iron and zinc supplementation in Indonesian infants: Effects on growth and development. Am J Clin Nutr 2004;80:729–36.
112. Black MM, Baqui AH, Zaman K, Ake PL, El Arifeen S, Le K, McNary SW, Parveen M, Hamadani JD, Black RE. Iron and zinc supplementation promote motor development and exploratory behavior among Bangladeshi infants. Am J Clin Nutr 2004;80:903–10.
113. Black MM, Sazawal S, Black RE, Khosla S, Sood M, Juyal RC, Menon V. Micronutrient supplementation leads to improved development and behavior among infants born small-for-gestational age. Pediatr Res 2002;51:2565.
114. Olney DK, Pollitt E, Kariger PK, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Stoltzfus RJ. Combined iron and folic acid supplementation with or without zinc reduces time to walking unassisted among Zanzibari infants 5- to 11-mo old. J Nutr 2006;136:2427–34.
115. Faber M, Kvalsvig JD, Lombard CJ, Benade AJ. Effect of a fortified maize-meal porridge on anemia, micronutrient status, and motor development of infants. Am J Clin Nutr 2005;82:1032–9.
116. Rao R, Georgieff MK. Perinatal aspects of iron metabolism. Acta Paediatr Suppl 2002;91:124–9.
117. World Health Organization. Global database on child growth and malnutrition. Geneva: WHO, 1998.
118. Administrative Committee on Coordination/Sub-Committee on Nutrition (ACC/SCN). Fourth Report on the World Nutrition Situation. Geneva: ACC/SCN in collaboration with IFPRI, 2000.
119. Allen LH. Anemia and iron deficiency: Effects on pregnancy outcome. Am J Clin Nutr 2000;71(5 suppl): 1280S–4S.
120. Halvorsen S. Iron balance between mother and

infant during pregnancy and breastfeeding. Acta Paediatr 2000;89:625–7.
121. Agrawal RM, Tripathi AM, Agarwal KN. Cord blood haemoglobin, iron and ferritin status in maternal anaemia. Acta Paediatr Scand 1983;72:545–8.
122. Chockalingam UM, Murphy E, Ophoven JC, Weisdorf SA, Georgieff MK. Cord transferrin and ferritin values in newborn infants at risk for prenatal uteroplacental insufficiency and chronic hypoxia. J Pediatr 1987;111:283–6.
123. Armony-Sivan R, Eidelman AI, Lanir A, Sredni D, Yehuda S. Iron status and neurobehavioral development of premature infants. J Perinatol 2004;24:757–62.
124. Vaughn J, Brown J, Carter JP. The effects of maternal anemia on infant behavior. J Natl Med Assoc 1986;78:963–8.
125. Wachs TD, Pollitt E, Cuerto S, Jacoby E, Creed-Kanishiro H. Relation of neonatal iron status to individual variability in neonatal temperament. Dev Psychobiol 2005;46:141–53.
126. Perez EM, Hendricks MK, Beard JL, Murray-Kolb LE, Berg A, Tomlinson M, Irlam J, Isaacs W, Njengele T, Sive A, Vernon-Feagans L. Mother-infant interaction and infant development are altered by maternal iron deficiency anemia. J Nutr 2005;135:850–5.
127. Camp BW, Broman SH, Nichols PL, Leff M. Maternal and neonatal risk factors for mental retardation: Defining the 'at-risk' child. Early Hum Dev 1998;50:159–73.
128. Georgieff MK, Petry CD, Wobken JD, Oyer CE. Liver and brain iron deficiency in newborn infants with bilateral renal agenesis (Potter's syndrome). Pediatr Pathol Lab Med 1996;16:509–19.
129. Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK. Iron deficiency of liver, heart, and brain in newborn infants of diabetic mothers. J Pediatr 1992;121:109–14.
130. Georgieff MK, Landon MB, Mills MM, Hedlund BE, Faassen AE, Schmidt RL, Ophoven JJ, Widness JA. Abnormal iron distribution in infants of diabetic mothers: Spectrum and maternal antecedents. J Pediatr 1990;117:455–61.
131. Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol 1995;173:1753–8.
132. Winer EK, Tejani N. Four- to seven-year evaluation in two groups of small-for-gestational-age infants. In: Tejani N, ed. Obstetric events and developmental sequelae, 2nd ed. Boca Raton, Fla, USA: CRC Press, 1994:77–94.
133. Strauss RS, Dietz WH. Growth and development of term children born with low birth weight: Effects of genetic and environmental factors. J Pediatr 1998;133:67–72.
134. Nelson CA, Wewerka SS, Borscheid AJ, deRegnier RA, Georgieff MK. Electrophysiologic evidence of impaired cross-modal recognition memory in 8-month-old infants of diabetic mothers. J Pediatr 2003;142:575–82.
135. Nelson CA, Wewerka S, Thomas KM, Tribby-Walbridge S, deRegnier RA, Georgieff M. Neurocognitive sequelae of infants of diabetic mothers. Behav Neurosci 2000;114:950–6.
136. DeBoer T, Wewerka S, Bauer PJ, Georgieff MK, Nelson CA. Explicit memory performance in infants of diabetic mothers at 1 year of age. Dev Med Child Neurol 2005;47:525–31.
137. Golub MS, Hogrefe CE, Germann SL, Capitano JL, Lozoff B. Behavioral consequences of developmental iron deficiency in infant rhesus monkeys. Neurotoxicol Teratol 2006;28:3–17.
138. Golub MS, Hogrefe CE, Tarantal AF, Germann SL, Beard JL, Georgieff MK, Calatroni A, Lozoff B. Diet-induced iron deficiency anemia and pregnancy outcome in the rhesus monkey. Am J Clin Nutr 2006;83:647–56.
139. Lubach GR, Coe CL. Preconception maternal iron status is a risk factor for iron deficiency in infant rhesus monkeys (*Macaca mulatta*). J Nutr 2006;136:2345–9.
140. Ronnenberg AG, Wood RJ, Wang X, Xing H, Chen C, Chen D, Guang W, Huang A, Wang L, Xu X. Preconception hemoglobin and ferritin concentrations are associated with pregnancy outcome in a prospective cohort of Chinese women. J Nutr 2004;134:2586–91.