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Iron requirements of infants and toddlers — Source link

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Abstract: Iron deficiency (ID) is the most common micronutrient deficiency worldwide and young children are a special risk group because their rapid growth leads to high iron requirements. Risk factors associated with a higher prevalence of ID anemia (IDA) include low birth weight, high cow's-milk intake, low intake of iron-rich complementary foods, low socioeconomic status, and immigrant status. The aim of this position paper was to review the field and provide recommendations regarding iron requirements in infants and toddlers, including those of moderately or marginally low birth weight. There is no evidence that iron supplementation of pregnant women improves iron status in their offspring in a European setting. Delayed cord clamping reduces the risk of ID. There is insufficient evidence to support general iron supplementation of healthy European infants and toddlers of normal birth weight. Formula-fed infants up to 6 months of age should receive iron-fortified infant formula, with an iron content of 4 to 8 mg/L (0.6-1.2 mg(-1) · kg(-1) · day(-1)). Marginally low-birth-weight infants (2000-2500 g) should receive iron supplements of 1-2 mg(-1) · kg(-1) · day(-1). Follow-on formulas should be iron-fortified; however, there is not enough evidence to determine the optimal iron concentration in follow-on formula. From the age of 6 months, all infants and toddlers should receive iron-rich (complementary) foods, including meat products and/or iron-fortified foods. Unmodified cow's milk should not be fed as the main milk drink to infants before the age of 12 months and intake should be limited to <500 mL/day in toddlers. It is important to ensure that this dietary advice reaches high-risk groups such as socioeconomically disadvantaged families and immigrant families.

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Iron Requirements of Infants and Toddlers

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ABSTRACT

Iron deficiency (ID) is the most common micronutrient deficiency worldwide and young children are a special risk group because their rapid growth leads to high iron requirements. Risk factors associated with a higher prevalence of ID anemia (IDA) include low birth weight, high cow's-milk intake, low intake of iron-rich complementary foods, low socioeconomic status, and immigrant status. The aim of this position paper was to review the field and provide recommendations regarding iron requirements in infants and toddlers, including those of moderately or marginally low birth weight. There is no evidence that iron supplementation of pregnant women improves iron status in their offspring in a European setting. Delayed cord clamping reduces the risk of ID. There is insufficient evidence to support general iron supplementation of healthy European infants and toddlers of normal birth weight. Formula-fed infants up to 6 months of age should receive iron-fortified infant formula, with an iron content of 4 to 8 mg/L (0.6–1.2 mg · kg^{-1} · day^{-1}). Marginally low-birth-weight infants (2000–2500 g) should receive iron supplements of 1–2 mg · kg^{-1} · day^{-1}. Follow-on formulas should be iron-fortified; however, there is not enough evidence to determine the optimal iron concentration in follow-on formula. From the age of 6 months, all infants and toddlers should receive iron-rich (complementary) foods, including meat products and/or iron-fortified foods. Unmodified cow's milk should not be fed as the main milk drink to infants before the age of 12 months and intake should be limited to <500 mL/day in toddlers. It is important to ensure that this dietary advice reaches high-risk groups such as socioeconomically disadvantaged families and immigrant families.

Key Words: anemia, breast-feeding, complementary feeding, cow's milk, follow-on formula, infant formula, infant, iron deficiency, iron requirements, low birth weight, toddler

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Iron deficiency (ID) is the most common micronutrient deficiency worldwide and young children are a special risk group because their rapid growth leads to high iron requirements. Risk factors associated with a higher prevalence of ID anemia (IDA) include low birth weight, high cow's-milk intake, low intake of iron-rich complementary foods, low socioeconomic status, and immigrant status (1–5).

Ten years ago, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition (CoN) published a commentary on iron requirements in early childhood, concluding that there was a lack of evidence regarding the health effects of different iron intakes (6). That comment did not include a recommendation regarding iron intakes.

The aim of this position paper is to review the field (see summary in Table 1) and provide recommendations regarding iron requirements of infants and toddlers (1–3 years of age), including those of moderately or marginally low birth weight. Recommendations for infants with a birth weight <1800 g have been previously published by the ESPGHAN CoN (7).

Relevant publications were identified from the databases of PubMed, ISI Web of Science, and the Cochrane Library up to March 2013. A comprehensive review of all randomized controlled trials of iron interventions in infants and toddlers was performed.

DEFINITION OF ID AND IDA

ID is conventionally considered to develop in 3 stages: iron depletion, iron-deficient erythropoiesis, and IDA, which is defined as the combination of ID and anemia (low hemoglobin [Hb]). In the first stage, body iron stores are reduced, which is typically measured using serum ferritin. This biomarker has been shown to closely parallel the size of body iron stores in adults, as measured by bone marrow staining or repeated phlebotomy. No similar validation studies have been performed in infants or toddlers. Serum ferritin is an acute-phase reactant, limiting its usefulness for the diagnosis of ID in states of infection or inflammation. Measurements of serum iron alone provide little useful information with regard to iron status because of the considerable hour-to-hour and day-to-day variation. Transferrin saturation (the ratio between serum iron and transferrin) is a more reliable marker than serum iron and will decrease in the first or second stage of ID. However,

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TABLE 1. Summary of conclusions

Definitions of IDA	A combination of hemoglobin and ferritin is recommended. Age-specific cutoffs should be used, see Table 2.
General prevalence of IDA in European infants and toddlers	<2% before 6 mo, 2%–3% at 6–9 mo, and 3%–9% at 1–3 y of age
Theoretical iron requirements	Low before 6 months of age 0.9–1.3 mg · kg^{-1} · day^{-1} at 6–12 mo 0.5–0.8 mg · kg^{-1} · day^{-1} at 1–3 y
Iron absorption	Generally low, depends on diet, but infants and toddlers can upregulate absorption when iron stores decrease
Health effects related to iron deficiency	IDA in young children is associated with long-lasting poor neurodevelopment
Adverse effects of excessive iron	Possibly poor growth, increased risk of infections, and even poor neurodevelopment
Iron supplementation of pregnant women	Does not improve infant iron status in European setting
Delayed umbilical cord clamping	Improves iron status of infants
Breast-fed infants <6 mo	Iron supplements do not reduce IDA in populations with already low (<5%–10%) prevalence of IDA at 6 months
Formula-fed infants <6 mo	Iron-fortified formula prevents IDA and possibly improves neurodevelopment
Low-birth-weight infants <6 mo	Iron supplements (1–3 mg · kg^{-1} · day^{-1} depending on birth weight) prevent IDA and possibly improve neurodevelopment
Follow-on formulas 6–12 mo	Iron fortification prevents IDA. Conflicting evidence with regard to neurodevelopment
Complementary foods 4–12 mo	Iron-rich complementary foods and avoidance of unmodified cow's milk prevents IDA
Iron supplements 4–12 mo	Prevents IDA and may improve neurodevelopment but only in populations with high (>10%) prevalence of IDA at 6–12 mo of age
Toddlers (12–36 mo)	Few studies, but iron-rich complementary foods and a restriction of unmodified cow's-milk intake to <500 mL may prevent IDA

IDA = iron-deficiency anemia.

ferritin is more commonly used than transferrin saturation as a marker of iron depletion.

In the second stage of ID, iron-deficient erythropoiesis, soluble transferrin receptors will increase in plasma as a marker of increased iron needs in body tissues. Furthermore, zinc protoporphyrin in red blood cells will increase, whereas the concentration of hemoglobin in reticulocytes will decrease. In the third stage of ID, IDA, the blood hemoglobin concentration will be reduced and red cell morphology will be affected; the mean cell volume will decrease, and the red cell distribution width will increase.

There are several novel indicators of ID that need further evaluation in children, including reticulocyte hemoglobin and hepcidin (8,9). Hepcidin is a newly characterized oligopeptide that seems to be pivotal for iron metabolism and it has been shown to be closely associated with iron status and iron intakes in infants (10).

ID is usually defined using ≥1 of the available markers of iron status. As discussed, there is a plethora of markers of iron status and none of them is sufficiently validated in children. Furthermore, reference ranges and cutoffs for the different iron status biomarkers are poorly defined in young children and the use of cutoffs defined for older ages is usually inappropriate for young children because of the large physiological changes in iron status and red cell morphology occurring during the first year of life (11).

The combination of Hb and ferritin is considered the most sensitive measure of the effects of iron interventions in children and adults (12). Globally, many prevalence studies of ID have been based on hemoglobin measurements only, assuming that ID causes approximately 50% of anemia cases worldwide (13,14); however, this does not produce reliable estimates because there are many other causes of anemia, the prevalence of which vary greatly between populations. Age-specific cutoffs for iron status indicators, including hemoglobin and ferritin, should be used for young children (Table 2).

PREVALENCE OF ID AND IDA

Globally, it is estimated that approximately 25% of preschool children have IDA (15). The prevalence of IDA in European infants is typically <2% before the age of 6 months, approximately 2% to 3% at 6 to 9 months, and 3% to 9% at 1 to 3 years of age (16–18) (4,19–21). Similarly, the prevalence of ID (usually defined as serum ferritin <10–12 μg/L) is highest at 1 to 3 years of age, whereas European prevalence figures usually vary between 5% and 20% (4,18–20).

THEORETICAL IRON REQUIREMENTS

Body composition studies in the 1950s showed that total body iron at birth is approximately 75 mg/kg (22). In the neonate, most of the body iron is found in hemoglobin, but a term, healthy, normal birth weight infant also has some iron stores, corresponding to approximately 25% of total body iron. When the newborn emerges from the relatively hypoxic environment of the uterus out into the oxygen-rich atmosphere, hemoglobin synthesis is halted and the Hb falls from an average of 170 g/L to about 120 g/L during the first 6 weeks of life (23). Because of recirculation of iron from senescent erythrocytes, iron is transferred from hemoglobin to iron stores, which thereby increase in size. During the following months, as the baby continues to grow and expand its blood volume, iron is transferred back from stores to the blood compartment, making the normal infant self-sufficient with regard to iron until the infant has doubled his or her birth weight, which occurs at about 4 to 6 months of age in a term, normal-birth-weight infant (23). Thus, exclusive breast-feeding during this period can meet infant iron requirements despite the low concentration of iron in breast milk (0.3 mg/L).

Between 6 and 24 months of age, the infant becomes dependent on additional dietary iron and, because of rapid growth, iron requirements per kilogram body weight are higher than during any other period of life. Using a factorial approach similar to the one published by Oski et al (24), assuming an average body weight of

TABLE 2. Suggested cutoffs for definition of anemia and low serum ferritin at different ages

	0–1 wk	2 mo	4 mo	6–24 mo	2–5 y
Hb, g/L	135	90	105	105	110
s-Ferritin, μg/L	40	40	20	10–12	10–12

Exact cutoffs for ferritin will vary depending on the laboratory method used. Data adapted from references 11 and 116–119.

7.5 kg at 6 months and 12 kg at 24 months, a blood volume of 80 mL/kg, tissue iron of 7 mg/kg, and iron stores of 10 mg/kg at 24 months, it can be calculated that total body iron needs to double from 300 to 600 mg between 6 and 24 months. Allowing for physiological iron losses of 20 $\mu g \cdot kg^{-1} \cdot day^{-1}$, the theoretical requirement of absorbed iron during this period is 0.076 $mg \cdot kg^{-1} \cdot day^{-1}$, which corresponds to an iron intake of 0.76 $mg \cdot kg^{-1} \cdot day^{-1}$, assuming an average bioavailability of 10%. After 2 years of age and up to puberty, iron requirements per kilogram of body weight are slightly lower because body growth is slower.

Different authorities recommended the following daily iron intakes: 7.8 to 11 mg at 6 to 12 months, 5.8 to 9.0 mg at 1 to 3 years, 6.1 to 10 mg at 4 to 8, and 8 to 11 mg/d at 9 to 13 years, corresponding to 0.9 to 1.3, 0.5 to 0.8, 0.3 to 0.5, and 0.2 to 0.3 $mg \cdot kg^{-1} \cdot day^{-1}$ (25–30).

IRON ABSORPTION

Because iron cannot be excreted from the body, intestinal absorption of iron is strictly regulated. Some food components promote nonheme iron absorption (ascorbic acid, citric acid, meat proteins, and human milk), whereas others inhibit absorption (phytates, polyphenols, calcium, and cow's milk). Absorption of nonheme iron from breast milk is usually assumed to be up to 50% and absorption from infant formula and iron-fortified complementary foods is usually assumed to be approximately 10% (23). Meat products contain heme iron, which has a bioavailability of approximately 25% and meat also promotes nonheme iron absorption (31); however, iron absorption is highly dependent on the individual's iron status. In a state of iron sufficiency, hepcidin is produced in the liver, and circulating hepcidin is believed to block basolateral iron release from enterocytes by inhibiting the iron transporter ferroportin. In contrast, in a state of ID, hepcidin levels decrease and intestinal iron absorption is increased. This regulation has been shown in animal models (32) and recently also in human infants (10). In line with this, it has been shown that infants have the ability to upregulate iron absorption when iron requirements increase (33,34). This ability of each individual to be able to adapt iron absorption to iron status is likely to make infants more resistant to ID than the factorial approach would predict and highlights the need for intervention trials to determine iron requirements.

HEALTH EFFECTS RELATED TO ID

The main public health problem associated with ID in childhood is the risk of poor neurodevelopment; however, some other physiological manifestations have been attributed to ID in young children, including growth retardation and impaired immune response. Even though a few studies have showed improved weight or length gain after iron treatment of initially iron-deficient children (35–37), most studies have found no overall positive effect of iron on growth (38) and, indeed, some studies have shown a negative effect of iron on growth in iron-replete infants (see below). Iron has many important functions in the immune system, and ID has been suggested to impair secretion of cytokines, and reduce bactericidal macrophage activity and T-cell proliferation (39); however, it has not been convincingly shown in clinical studies that ID increases the risk of infections. On the contrary, iron supplements have in several studies been associated with an increased risk of infections (see below).

EFFECTS ON NEURODEVELOPMENT

Growth and development of the central nervous system is rapid during the first years of life and iron is critical for this process. The human brain almost triples its weight from birth to 3 years of age and has at that age reached 85% of its adult size (40). Animal studies have shown that iron is essential for several aspects of brain development: myelination, monoamine neurotransmitter function, neuronal and glial energy metabolism, and hippocampal dendritogenesis (41,42).

Several well-performed case-control studies in children have shown a consistent association between IDA in infancy and long-lasting poor cognitive and behavioral performance (43,44). A seminal case-control study was performed in the 1980s by Lozoff et al, in a cohort of 191 Costa Rican 12- to 23-month-old toddlers who had varying degrees of ID. She observed that toddlers with IDA (defined as Hb <100 g/L and a serum ferritin <12 μg/L in combination with either a high zinc protoporphyrin or a low transferrin saturation) attained poorer Bayley mental development score by an average of 8 points and poorer Bayley psychomotor development score by an average of 10 points compared with nonanaemic children. Lower cognitive scores compared with controls remained at 5 (45), 11 to 14 (46), and up to 19 years of age (47), despite early iron therapy. These results were statistically adjusted for environmental and family factors, but the possibility of residual confounding by socioeconomic or nutritional factors cannot be excluded. Other case-control studies have shown similar results with regard to cognitive performance (48,49), latencies of evoked potentials (50,51), and motor development (52). Children with IDA also have been shown to have long-lasting behavioral problems, including wariness, hesitance, and externalizing and internalizing problems (53).

It has been suggested that ID without anemia may be associated with poor cognitive/behavioral outcomes, but this has not been sufficiently studied. In particular, there is a lack of dose-response studies linking indicators of iron status as continuous risk factors with later cognitive outcomes.

A meta-analysis of 17 randomized clinical trials in children that included cognitive outcomes showed that iron supplementation had a modest positive effect on mental development indices, equivalent to 1.5 to 2 points of 100, measured at the end of the intervention (54). This effect was more apparent for children who were initially anemic or who had IDA, suggesting that iron supplements have positive cognitive effects in iron-deficient children. This meta-analysis showed a more pronounced effect in children ages 7 years or older and no convincing evidence for an effect of iron supplements on neurodevelopmental outcomes in children younger than 2 years. This lack of effect in the youngest infants may be because of irreversible effects of ID on the developing brain or the fact that cognitive development and behavior are more difficult to measure in young children.

A recent meta-analysis concluded that preventive iron supplements in infancy have a positive effect on motor development (55), although this conclusion was reached based on the data from only 3 randomized controlled trials (56–58).

POSSIBLE ADVERSE EFFECTS OF IRON

It is important to note that iron is a potent pro-oxidant and that iron, in contrast to most other nutrients, cannot be actively excreted by humans (23). In adults, the risk of iron overload from dietary iron is mainly limited to individuals with hereditary hemochromatosis, a relative common disorder especially in northern Europe, with a reported frequency of homozygosity for the C282Y mutation of approximately 0.3% and even higher prevalences in Ireland, the United Kingdom, and Scandinavia (59); however, in children, the risk of iron overload must be considered also in individuals without this genetic disposition. Iron supplementation of iron-replete infants may have adverse effects, for example, increased risk of infections and impaired growth (60). Increased risk of severe infections seems to be restricted to malarious regions (61), whereas the risk of impaired growth has been observed also in European infants in one study, which reported a 0.6-SD difference in length gain between 4 and 9 months of age (62). A negative effect of iron supplements on growth in iron-replete young children has been shown in some studies (62–65) but needs confirmation in larger trials and has not yet been confirmed in meta-analyses (38).

Because high iron intakes may have adverse effects in iron-replete infants, it is important to identify iron requirements in young children and to identify risk groups that benefit from higher iron intakes.

PREVENTION OF ID

Risk factors for ID and IDA in European infants and toddlers include low birth weight, early cord clamping, male sex, low socioeconomic status, low meat intake, low intake of iron-fortified products (including infant formula and follow-on formula), and a high intake of cow's milk (4,18–20,66–68).

Suggested interventions for prevention of ID at different ages include iron supplementation of pregnant women, delayed umbilical cord clamping, iron supplementation of infants (iron drops), iron-fortified formula, meat products, iron fortification of follow-on formula and complementary foods, avoidance of cow's milk, and use of iron-fortified milks. The following is a review of the available evidence from intervention trials regarding these different approaches.

IRON SUPPLEMENTATION OF PREGNANT WOMEN

Iron supplementation of pregnant women has been suggested to improve iron status in the newborn; however, iron transport to the fetus is an active process and the fetus may be protected from ID even when the mother has mild or moderate IDA. A recent systematic review (69) concludes that there is a lack of convincing evidence that iron supplementation during pregnancy improves infant iron status, even though improvement was reported by a single study performed in an Nigerian population with an extremely high prevalence of IDA (70).

The ESPGHAN CoN concludes that there is no convincing evidence that iron supplementation of pregnant women in a European setting would improve infant iron status.

UMBILICAL CORD CLAMPING

The timing of umbilical cord clamping is of great importance for the amount of blood transfused from the placenta to the newborn and may therefore influence the risk of later ID and IDA. Studies in the 1960s showed that in normal, term newborns held 10 cm below the vaginal level, the placental transfusion during the first 3 minutes of life increases the newborn's blood volume on average by 32% (71). These studies also showed that a similar transfusion occurs when the baby is placed on the mother's chest (71). A recent European survey of policies at different delivery units showed large differences in cord clamping times both between and within countries (72). Early cord clamping has been suggested to reduce the risk for maternal postpartum hemorrhage.

Andersson et al (67) randomized 400 term Swedish infants to delayed (>3 minutes) or early (<10 seconds) cord clamping and showed a significant effect on neonatal iron status and also a significant reduction in the proportion of iron-deficient infants at 4 months of age (0.6% vs 5.7%, $P = 0.01$), without any increase in neonatal jaundice or any other adverse effects. Furthermore, there were no adverse effects on postpartum hemorrhage or the proportion of accurate umbilical cord blood gas samples (73). These results support the conclusions of a Cochrane analysis, based on studies performed in low-income countries, which concluded that late cord clamping improves infant iron status (74).

There is strong evidence that delayed cord clamping improves the iron status of infants and no convincing evidence that this has any adverse effects. Compared with dietary interventions, this practice is also easy to implement on a population level. The ESPGHAN CoN therefore recommends delayed cord clamping for all newborns.

DIETARY INTERVENTION STUDIES

Breast-Fed Infants

Iron supplements (ie, iron drops) are usually not recommended for healthy, term, breast-fed infants during the first months of life; however, 2 recent studies have addressed this issue. In a study by Friel et al, 77 term, normal-birth-weight, breast-fed Canadian infants were randomized to receive iron supplements (7.5 mg/day, corresponding to 1–2 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) or placebo between 1 and 6 months of life (56). Infants in the iron group had significantly higher Hb at 6 months (124 vs 116 g/L), but this difference had disappeared at 12 months. The prevalence of IDA at 6 months was 14% (3/21 infants) in the placebo group versus 0% (0/28) in the iron-supplemented group, but this difference was not significant because of the low number of infants in the study. It is notable that the IDA prevalence of 14% at 6 months in this study was higher than in most other studies of exclusively breast-fed infants. In a follow-up at 13 months of age, iron-supplemented infants had significantly higher Bayley psychomotor development index (PDI) (100 ± 12 vs 93 ± 9); however, a weakness with this study was small sample size and high attrition; of the original 77 infants, only 37 were evaluated at 13 months. These results need to be confirmed in an adequately powered study before they can form the basis for recommendations.

Ziegler randomized 75 term, normal-birth-weight, breast-fed infants to receive a multimicronutrient supplement with or without iron (7 mg/day corresponding to 1–2 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}) from 1 to 5.5 months of age (75). Infants receiving iron had significantly higher plasma ferritin at 5.5 months, but there was no difference in the primary outcome, which was serum ferritin at 9 months of age. The prevalence of IDA at 6 months in this study was 3% (1/29) versus none in the iron-supplemented group. In this trial, no neurodevelopmental outcomes were included.

The ESPGHAN CoN concludes that there is no convincing evidence that iron supplements should be provided to normal-birth-weight, exclusively breast-fed infants during the first 6 months

of life in populations with a low prevalence of IDA among 6-month-olds.

Formula-Fed Infants Up To 6 Months

The importance of iron fortification of infant formula for the prevention of IDA in infants was demonstrated in the 1950s (76) and has since been confirmed (77). In 1994, Moffatt et al published a comprehensive study in which 283 Canadian infants from extremely low-income families were randomized to an iron-fortified infant formula (12.8 mg/L) or a nonfortified formula (1.1 mg/L of iron) from <2 to 15 months of age (58). At 6 months, infants receiving iron-fortified formula had significantly higher mean Hb (113.5 vs 107.7 g/L) and serum ferritin (26.8 vs 15.7 μg/L). There was a significantly lower proportion of anemia (Hb <110 g/L) at 6 months in the iron-fortified group (8% vs 28%, $P < 0.001$). At 9, 12, and 15 months of age, these differences in iron status remained but became more attenuated with time. Neurodevelopment was assessed using the Bayley scales of infant development at 6, 9, 12, and 15 months of age. The PDI was similar between groups at 6 months but fell in the unfortified group at 9 and 12 months with a trend toward recovery at 15 months. At 12 months, mean (±SD) PDI among infants in the iron-fortified group was 100.5 ± 14.1 as compared with 94.2 ± 12.6 in the unfortified group, $P = 0.002$. There was no significant difference in the mental development index at any time point. This study confirms the importance of iron fortification of infant formula, even though the population of poor infants with a high prevalence of anemia at 6 months even in the iron-fortified group is not representative of the present European population.

Owing to the much lower bioavailability of iron from infant formula compared with breast milk, infant formulas have traditionally been fortified to higher iron concentrations than in breast milk; however, there has been a long-standing controversy regarding which is the optimal level of iron fortification of infant formulas; present American guidelines suggest 10 to 12 mg/L (78), whereas the ESPGHAN-coordinated global standard recommends 0.3 to 1.3 mg/100 kcal, corresponding to 2 to 8.5 mg/L (79). As a comparison, the iron content of breast milk is approximately 0.3 mg/L (80). The higher level of 12 mg/L is based on the theoretical iron requirements from 0 to 12 months, but does not take into account that the iron requirements during the first 6 months of life are extremely low, as explained above. The lower level of 2 mg/L is based on the iron content in breast milk and the assumed difference in iron bioavailability between breast milk and infant formula, but this level has not yet been shown to be safe in sufficiently powered intervention trials.

A few studies have compared the effects of different levels of iron fortification of infant formula during the first 6 months of life. In 1993, Bradley et al (81) randomized 347 healthy US infants to receive infant formulas containing 7.4 or 12.7 mg/L of iron from <2 to 12 months of age. There was no difference in Hb or serum ferritin between groups at 6 months of age.

In 1994, Lönnerdal and Hernell (82) randomized 50 Swedish infants to 5 different intervention groups. Forty of the infants received formulas with iron contents of 3.8 to 4.7 mg/L and 10 received a formula with an iron content of 6.9 mg/L. The intervention lasted from <2 to 6 months of age. At 6 months, there were no differences between high- and low-iron formula groups in Hb or ferritin and no infant had ferritin <12 μg/L.

During the last decade, 2 studies have been performed using even lower levels of iron fortification during the first 6 months of life. In a British study, 100 healthy, term, normal-birth-weight infants were randomized to receive formula with either 5 or <1 mg/L of iron from the first week of life until 3 months of age (83). There was no difference in Hb, ferritin, or any other iron status variable between the groups at 3 or 12 months of age. In a Swedish study, 43 term, normal-birth-weight infants were randomized to different infant formulas with iron concentrations ranging from 2 to 4 mg/L from 1 to 6 months of age (84). No significant difference in iron status was observed at 6 months; however, neither of these studies was powered to study effects on ID or IDA. Even though these studies suggest that iron concentrations lower than those commonly used may be sufficient during the first few months of life, no conclusion can be made regarding whether such low iron concentrations will effectively prevent ID in the European populations.

Presently, most standard infant formulas in Europe have iron concentrations of 4 to 8 mg/L. Based on the above evidence and the low prevalence of IDA at 6 months in Europe, the ESPGHAN CoN considers this practice safe and effective, but there is clearly a need for sufficiently powered randomized controlled studies to better determine the appropriate level of iron in infant formulas, which may very well be lower than this range.

Low-Birth-Weight Infants

Low birth weight (LBW), defined as birth weight <2500 g, is a major public health problem. In 2009, UNICEF estimated the global prevalence to be 14% and local prevalence varies between 5% (Sweden) and 28% (India) (85). LBW is associated with increased neonatal mortality and morbidity and is also an important risk factor for lifelong health problems, including cognitive and behavioral problems (86). LBW infants include both term, small-for-gestational-age infants and preterm infants. Most LBW infants have only marginally or moderately LBW (1500–2500 g). Infants in this weight interval rarely require neonatal intensive care, and clinical practice regarding iron supplementation of these infants is highly variable (87). LBW infants have lower total body iron at birth and a more rapid relative growth rate, leading to high iron requirements even before 6 months of age. Using a similar factorial calculation as above, an infant with a birth weight of 2000 g will theoretically need at least 1 $mg \cdot kg^{-1} \cdot day^{-1}$ of dietary iron between 6 weeks and 6 months of life.

There are relatively few published randomized intervention trials comparing different doses of iron supplements or fortification of human milk or formula given to LBW infants.

A meta-analysis has shown that prophylactic iron (supplements or iron-fortified formula) given to LBW infants, with birth weights 1500 to 2500 g, leads to significantly reduced incidence of anemia at 6 months (88). Most of these studies used an enteral iron dose of 2 $mg \cdot kg^{-1} \cdot day^{-1}$.

There are even fewer studies comparing different amounts of iron given to LBW infants. In a study by Friel et al, 58 infants with an average birth weight of 1500 g were randomized to different infant formulas resulting in iron intakes of 3 to 6 vs 2 to 3 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 9 months of age (89). There was no difference in anemia or neurodevelopment at 12 months; however, the high-iron group had higher glutathione peroxidase concentrations (a marker of oxidative stress), lower plasma zinc and copper concentrations, and a higher number of respiratory tract infections, suggesting possible adverse effects with higher iron intakes.

In a recent trial, Berglund et al randomized 285 marginally LBW Swedish infants (2000–2500 g) to iron supplements at the following doses: 0 (placebo), 1 or 2 $mg \cdot kg^{-1} \cdot day^{-1}$, given from 6 weeks to 6 months of age. In this population, iron supplements at a dose of 2 $mg \cdot kg^{-1} \cdot day^{-1}$, compared with placebo, significantly reduced the risk of IDA at 6 months (66). In the placebo group, 36%

developed ID and 10% developed IDA, as compared with 4% and 0% in the 2-mg group. Approximately half of these infants were mostly breast-fed during the intervention and the other half received iron-fortified formula. No adverse effects of iron supplements were observed with regard to infant growth, infections, or other morbidity. There were significant differences in iron status between those who had received 1 or 2 mg · kg^{-1} · day^{-1} of iron, but there were no significant differences in the proportion of infants with ID or IDA in the 2 groups. When considering all dietary iron sources and iron supplements, including compliance, it was shown that an actual iron intake of 0.25 mg · kg^{-1} · day^{-1} was sufficient to prevent IDA and an intake of 1 mg · kg^{-1} · day^{-1} prevented ID (66). In a follow-up of this study, a significantly higher proportion of abnormal behavioral scores at 3.5 years of age was observed in the placebo group (89a). Using a validated questionnaire (Achenbach Child Behavior Checklist), the prevalence of children with behavioral scores above the US subclinical cutoff was 12.7%, 2.9%, and 2.7% in the placebo, 1-mg, and 2-mg group, respectively, as compared with 3.2% in a reference group of children with normal birth weight. Adjusting for socioeconomic confounders, the risk of behavioral problems was 4.5 times higher (95% confidence interval [CI] 1.3–15.8) in placebo-treated compared with iron-supplemented children; however, no significant differences were observed in cognitive scores.

Previously published guidelines recommend an iron intake of 2 to 3 mg · kg^{-1} · day^{-1} during the first 6 months of life for preterm infants with birth weights <1800 g (7).

The ESPGHAN CoN concludes that there is some evidence that iron supplements at a dose of 1 to 2 mg · kg^{-1} · day^{-1} given to infants with marginally LBW up to 6 months of age prevents IDA, without adverse effects, and reduces the risk for later behavioral problems.

Older Infants (From 4 to 6 Months of Age)

Because iron stores normally become depleted at approximately 6 months of age, iron-rich complementary foods are recommended. This includes meat products, iron-fortified follow-on formulas, and other iron-fortified foods, for example, cereals.

Follow-On Formulas

During the 1990s, several randomized controlled studies were performed, investigating the effects of different iron content in follow-on formulas on iron status and neurodevelopment. Gill et al (90) randomized 406 healthy infants in the United Kingdom and Ireland to receive a low-iron (1.4 mg/L) or high-iron (12.3 mg/L) formula from 6 to 15 months of age. Infants receiving the high-iron formula were significantly less likely to have low serum ferritin concentrations (<10 μg/L) at 15 months (6% vs 22%,) but there was no difference in the incidence of anemia (Hb <110 g/L), which was 11% vs 13%. The incidence of IDA and dietary intakes were not reported in this study.

Stevens et al (91) randomized 92 healthy UK infants to receive a no-added-iron formula or a formula containing 12 mg/L of iron from 6 to 18 months of life. Most of the children were from poorer socioeconomic groups. Throughout the study, there was no difference in mean Hb or median serum ferritin concentrations between groups. The proportion of infants with serum ferritin levels (<10 μg/L) at 12 to 18 months was 8% to 25% with no significant difference between groups. The proportion of infants with anemia (Hb <110 g/L) at 18 months was 15% in the low-iron group and 0% in the high-iron group, but this difference was not statistically significant. The prevalence of IDA and dietary intakes during the intervention were not reported.

Morley et al randomized 493 healthy UK infants to 3 interventions from 9 to 18 months of age: unmodified cow's milk, unfortified formula (0.9 mg/L), or iron-fortified formula (12 mg/L) (92). At 18 months, geometric mean plasma ferritin was significantly higher in the iron-fortified group (22 vs 13–14 μg/L). Hemoglobin values were only available in a subgroup of 38 infants. In that subgroup, mean Hb concentrations at 18 months were significantly higher in the iron-fortified group compared with the 2 other groups (126 vs 119–120 g/L). The proportion with anemia (Hb <110 g/L) at 18 months was 5% in the iron-fortified group, 11% in the unfortified group, and 32% in the cow's-milk group, but these differences were not statistically significant. The proportions with ID and IDA were not reported. There was no significant difference between groups in the primary outcome, which was Bayley mental and psychomotor development index at 18 months of age, tested in 428 infants. Intake data were reported in a separate study (93), showing that the mean (±SD) formula intake at 9 months was 530 ± 180 mL/day, corresponding to 6.2 mg/day of iron (approximately 0.7 mg · kg^{-1} · day^{-1}) from formula in the iron-fortified group. Similarly, formula intake at 12 months was 550 ± 220 mL/day, corresponding to 6.6 mg/day of iron (approximately 0.55 mg · kg^{-1} · day^{-1}).

Daly et al (94) randomized 100 UK infants from a poor socioeconomic area to receive iron-fortified formula (12 mg/L) or unmodified cow's milk from an average of 8 months to 18 months of age. By 18 months, 2% of the infants in the iron-fortified group and 33% of the infants in the cow's-milk group were anemic (Hb <110 g/L, $P < 0.001$). Average formula intake at 12 months was 582 mL/day, corresponding to 7 mg/day of iron (approximately 0.6 mg · kg^{-1} · day^{-1}) in the iron-fortified group. In addition, infants consumed on average of 5.3-mg/day iron from solid foods at 12 months. There was no significant difference in developmental score (Griffiths) at 18 months, but when 85% of the children were tested at 24 months of age, those in the iron-supplemented group had significantly higher developmental scores (Griffiths general quotient 102.2 vs 94.5, $P = 0.04$ for change since baseline) (95).

Walter et al randomized 835 healthy Chilean infants with birth weights >3 kg and no IDA at 6 months to high-iron (12 mg/L) or low-iron (2.3 mg/L) formula from 6 to 12 months. At 12 months, infants in the high-iron group had significantly higher serum ferritin concentrations and a significantly lower proportion had low ferritin (49% vs 65%); however, there was no significant difference in Hb at 12 months (125 vs 123 g/L). The proportion of IDA at 12 months was low (2.8% vs 3.8%), with no significant difference between groups (96). Mean (±SD) formula intake during the intervention was 616 ± 178 mL/day, corresponding to 7.4 mg/day of iron (approximately 0.8 mg · kg^{-1} · day^{-1}) in the high-iron group. The corresponding iron intakes in the low-iron group were 1.4 mg/day and 0.16 mg · kg^{-1} · day^{-1}. When 473 of these children were followed up at 10 years of age using several instruments, including the Wechsler Intelligence Scale for Children, spatial memory, arithmetic, visual motor integration, and motor coordination, there was a trend toward a lower IQ in the iron-fortified group (91.5 vs 93.3, $P = 0.06$), and the iron-fortified group had significantly lower scores with regard to spatial memory (86.8 vs 91.4, $P = 0.02$) and visual-motor integration (97.2 vs 99.8, $P = 0.046$) (97). Furthermore, there was a significant interaction between initial Hb at 6 months and the intervention effects on all developmental outcomes; children with higher 6-month Hb concentrations (>128 g/L) showed poorer developmental outcomes if they received iron-fortified formula, whereas those with low initial hemoglobin levels (<105 g/L) showed better outcomes with iron-fortified formula.

There is some evidence that iron-fortified follow-on formulas reduce the risk of anemia, especially when compared with unmodified cow's milk. There are conflicting results regarding the possible effects of iron-fortified follow-on formulas on neurodevelopment, with one study showing a positive effect in high-risk infants (94) and another showing a negative effect in iron-replete infants (97). The latter result is potentially alarming and requires confirmation.

A difficulty when assessing these studies is that the intake of follow-on formula is extremely variable because the infants also consume other foods. Using the average intakes from these studies (approximately 600 mL/day), an average weight of 8.8 kg at 9 months, a follow-on formula with 12 mg/L of iron will result in an iron intake of 0.8 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}, which is slightly lower than the recommended iron intake at this age; however, iron intake from other foods may not be negligible, as shown in the Daly et al study. Present European follow-on formulas usually contain 10 to 12 mg/L of iron. It is possible that iron fortification to lower concentrations may be safe and effective, but this requires further studies.

Based on the evidence from intervention trials, experience from present practice, and theoretical iron requirements, iron fortification of follow-on formulas is recommended. The European directive (98) allows iron fortification levels of follow-on formulas between 0.6 and 2 mg/100 kcal, corresponding to 3.6 to 14 mg/L. A recent international expert group recommends a level of 1.1 to 1.9 mg/100 kcal, corresponding to 6.6 to 13.3 mg/L (99); however, the ESPGHAN CoN concludes that there is not enough evidence to determine the optimal level of fortification, and it is unclear whether fortification to a higher level (10–14 mg/L) has any advantages.

Further studies are clearly warranted of different iron fortification levels of follow-on formula, including long-term follow-up of cognitive development. Furthermore, unmodified cow's milk should be avoided as the main milk drink in infants up to 12 months of age.

Meat Products and Iron-Fortified Complementary Foods

Meat products and iron-fortified foods are the major dietary sources of iron, and early introduction of these iron-rich complementary foods is therefore likely to be important for preventing ID and IDA in infants.

Several studies have evaluated the effects of iron-fortified complementary foods on iron status of older infants and toddlers. A recent meta-analysis included 18 randomized controlled trials of iron-fortified complementary foods, including cereals and fortified milks (n = 5468 children) (100). The median anemia rate at baseline was 36%, suggesting that these were not only purely preventive but also therapeutic trials. Mean age at inclusion was 6 to 23 months. There was a significant effect of iron-fortified complementary foods on hemoglobin (6.2 g/L higher than controls, 95% CI 3.4–8.9 g/L). Iron-fortified complementary foods reduced the risk of anemia (defined as Hb <105 or 110 g/L) by 50% (95% CI 0.33–0.75). A combination of iron and multimicronutrient fortification was more effective than iron fortification alone; however, these results are not directly generalizable to the European population because most of the trials were performed in low-income countries. Of the included trials, none evaluated iron-fortified cereals in a European or high-income country setting.

Jonsdottir et al (17) randomized 119 exclusively breast-fed infants at 4 months to continue exclusive breast-feeding or to introduce complementary foods to be given between 4 and 6 months of age. Infants receiving complementary foods had a median iron intake of 0.3 mg/day, corresponding to approximately 0.04 mg $\cdot$ kg^{-1} $\cdot$ day^{-1}. At 6 months, infants who had received iron-fortified complementary foods had significantly higher serum ferritin concentrations (median 70 vs 44 μg/L, $P = 0.02$), but there was no significant difference in Hb or other iron status indicators. There was no significant difference in the proportion of infants with low ferritin (<12 μg/L) at 6 months (10% vs 4% in complementary feeding vs exclusive breast-feeding group, respectively, $P = 0.44$). Only 2% of the infants were classified as IDA at 6 months, 1 in each randomization group.

In a Danish study, 41 healthy infants were randomized to a low-meat diet (10 g meat daily) or a high-meat diet (27 g meat daily) from 8 to 10 months of age (101). At 10 months, Hb was significantly higher among infants in the high-meat group (4 g/L difference, $P = 0.008$). No infant had IDA in this study.

Krebs et al randomized 88, exclusively breast-fed US infants to receive either pureed beef or iron-fortified infant cereal as their first complementary food from 5 to 7 months of age (102). Iron intakes were significantly higher in the cereal group (7.2 vs 1.5 mg/day) at 7 months. At 9 months of age, there was no significant difference in Hb or serum ferritin between groups. Forty percent of infants in the meat group and 30% of the infants in the cereal group had serum ferritin concentrations <12 μg/L. Anemia (Hb <115 g/L—taking the altitude of Denver, Colorado into consideration) was observed in 23% in the meat group and 15% in the cereal group. These differences in proportions of low ferritin or Hb were not statistically significant. The prevalence of IDA was not reported. Bayley developmental scores up to 12 months of age did not differ between groups.

In a Canadian study, 156 infants from low-income households were randomized to receive iron-rich complementary foods (iron-fortified cereals and pureed meat daily), in combination with whole cow's milk, or no intervention, from 6 to 12 months of age (103). At 12 months, 66% of the infants remained in the study. No significant differences in Hb, serum ferritin, or the proportion of infants with low serum ferritin (<10 μg/L) or anemia (Hb <110 g/L) were observed. The authors speculated that the high iron intake from complementary foods (average 98 g of meat daily) may be counteracted by the ad libitum cow's-milk intake in the intervention group (amounts not reported). In contrast, infants in the control group were either breast-fed or fed iron-fortified formula.

Dube et al (104) randomized 97 healthy German infants to receive commercial baby foods with high (12%) or low (8%) meat content from 4 to 10 months of age. Taking other complementary foods into account, total iron intakes did not differ between groups and there was no significant difference in Hb or serum ferritin. At 10 months, 4% had anemia (Hb <105 g/L) with no difference between intervention groups. IDA was not reported.

In summary, there is some evidence that complementary foods with a high meat content improve Hb. There is evidence from 1 study that a high meat intake has a similar effect on iron status as iron-fortified cereals, even though the daily iron intake in the cereal group was approximately 5 times higher. This is compatible with previous studies suggesting that iron absorption is several-fold higher from meat than from cereals (105).

Based on the evidence from intervention studies, clinical experience, and theoretical iron requirements, the ESPGHAN CoN recommends that iron-rich complementary foods (meat products and/or iron-fortified foods) should be given to all infants from 6 months of age.

Iron Supplements

Exclusive breast-feeding for 4 to 6 months is recommended by the ESPGHAN and other authorities; however, exclusive

breast-feeding beyond 6 months has been associated with increased risk of ID and IDA (106–108). It has therefore been suggested that iron supplements should be recommended for infants who are breast-fed for longer than 4 to 6 months and who do not consume enough iron from complementary foods. Indeed, the American Academy of Pediatrics recently suggested that iron supplements ($1\ mg \cdot kg^{-1} \cdot day^{-1}$) should be given from 4 months of age to all exclusively breast-fed infants and to partially breast-fed infants who receive more than half of their daily feeds as human milk (78). According to this recommendation, iron supplements of these infants should be continued ''until appropriate iron-containing complementary foods have been introduced'' (78). These American Academy of Pediatrics' recommendations have since been questioned (109,110).

There are several published randomized intervention trials, investigating the effects of iron supplements given to infants between 6 and 12 months of age, but almost all of these trials have been performed in low-income countries with a high prevalence of anemia among infants. These trials have generally shown that iron supplements reduce anemia, especially when given to anemic infants (60). Only a few of these trials have investigated the effects on neurodevelopmental outcomes: Lind et al randomized 340 Indonesian infants to receive iron supplementation (10 mg/day) or placebo from 6 to 12 months of age. These infants were healthy and none had severe anemia (<90 g/L), but 41% had mild anemia (Hb 90–110 g/L). At 12 months, infants receiving iron supplements had a significantly higher psychomotor developmental scores (106 vs 103, $P < 0.05$). In a Thai study, 560 infants ages 4 to 6 months were randomized to 4 groups, receiving daily iron (10 mg), zinc, iron plus zinc, or placebo for 6 months. In a follow-up study, no significant differences were observed at 9 years of age in cognitive performance (111); however, the prevalence of IDA during infancy was low (≤3%) in this sample.

To our knowledge, there has been only 1 randomized controlled trial investigating the effects of iron supplements given from 4 to 6 months of age to exclusively breast-fed infants in a European or high-income country setting (16). In this trial, 232 Swedish and Honduran infants were randomized into 3 groups: iron supplements from 4 to 9 months of age, iron supplements from 6 to 9 months of age, or no iron supplements. These infants were exclusively breast-fed to 6 months and mainly breast-fed between 6 and 9 months. In the Honduran subgroup, iron supplements from 4 to 6 months significantly reduced the prevalence of IDA at 9 months from 28% to 11% ($P = 0.006$); however, in the Swedish subgroup ($n = 101$), iron supplementation did not significantly reduce the already low prevalence of IDA at 9 months (<3% in all groups). Furthermore, in a secondary analysis among the Swedish infants in this study, iron supplements resulted in lower length gain with a difference of 0.4 cm between iron-supplemented and nonsupplemented infants up to 9 months of age ($P = 0.02$) (62).

There is strong evidence that iron supplementation of infants from 4 to 6 months of age reduces the prevalence of anemia in populations with a high prevalence of IDA in infants.

There is insufficient evidence that general iron supplementation of exclusively or mainly breast-fed infants from 4 to 6 months reduces IDA or has any other health benefits in populations with a low prevalence of IDA.

The ESPGHAN CoN does not recommend general iron supplementation of breast-fed European infants after the age of 4 to 6 months; however, preventive iron supplementation may be provided on an individual basis to infants from high-risk groups (low socioeconomic status or living in areas with high prevalence of IDA) if the infant has a low intake of iron-rich complementary foods.

Toddlers

Among all of the preadolescent age groups, the prevalence of IDA is highest among toddlers. IDA in toddlers can be prevented by ensuring adequate iron intake during the first year of life, but dietary interventions in toddlers have also been suggested and shown to be effective for prevention or reversal of IDA in low-income countries (112,113); however, extremely few iron intervention trials have been performed among toddlers in European or high-income countries.

In a Swedish trial, 36 healthy, iron-replete toddlers were randomized to receive iron-fortified (7.0 or 14.9 mg/L) or unfortified cow's milk from 12 to 18 months of age (114). There were no significant effects on iron status. At 18 months, the prevalence of ID (defined by multiple biomarkers) was low (11%). Only a single child had IDA at 18 months and that child belonged to the iron-fortified group.

In a New Zealand trial, 225 healthy, nonanemic 12- to 20-month-old toddlers were randomized to receive a high-meat diet, iron-fortified milk, or unmodified cow's milk during 5 months (115). There was a significant increase in serum ferritin (44%, $P = 0.002$) in the fortified milk group as compared with the meat group (10%) and the control group (−14%). Both the red meat group and the fortified milk group had a significant positive intervention effect with regard to serum ferritin. There were no significant differences between the 3 groups in the proportion of infants with low ferritin (<12 μg/L) or IDA (Hb <110 g/L in combination with other markers). The prevalence of IDA was ≤3% in all groups.

There is no evidence from randomized trials conducted in toddlers that dietary interventions prevent ID or IDA, nor that they have other health benefits in populations with a low IDA prevalence; however, as reported above, there are data from randomized controlled trials of follow-on formulas versus unmodified cow's milk, extending up to 18 months of age, suggesting that a high cow's-milk intake (average approximately 600 mL/day) increases the risk of IDA (92,94), and there are also data from European epidemiological studies suggesting that an intake of unmodified cow's milk exceeding approximately 450 mL/day is associated with an increased risk of ID (2,4).

The ESPGHAN CoN recommends that toddlers should receive iron-rich foods and that an intake of >500 mL/day of unmodified cow's milk should be avoided. It is up to national authorities to decide what type of iron-rich foods (eg, meat products, iron-fortified foods) should be encouraged in their own country, depending on food habits, and so on.

CONCLUSIONS AND RECOMMENDATIONS BY THE ESPGHAN CoN

These recommendations are valid for Europe and other regions with a low general prevalence of IDA.

1. There is no evidence that iron supplementation of pregnant women improves iron status in their offspring in a European setting.
2. Delayed cord clamping should be considered for all newborns.
3. There is no need for general iron supplementation of healthy European infants and toddlers of normal birth weight.
4. Formula-fed infants up to 6 months of age should receive iron-fortified infant formula, with an iron content of 4 to 8 mg/L.
5. Marginally-low-birth-weight infants (2000–2500 g) should receive iron supplements of $1–2\ mg \cdot kg^{-1} \cdot day^{-1}$, starting at 2 to 6 weeks of age and continuing to 6 months of age, regardless of whether they are term or preterm.

6. LBW infants with birth weights <2000 g should receive iron supplements at a dose of 2 to 3 mg/kg, according to ESPGHAN guidelines for enteral nutrition of preterm infants (7).
7. Follow-on formulas should be iron fortified; however, there is not enough evidence to determine the optimal iron concentration in follow-on formula.
8. From the age of 6 months, all infants and toddlers should receive iron-rich (complementary) foods, including meat products and/or iron-fortified foods.
9. Unmodified cow's milk should not be fed as the main milk drink to infants before the age of 12 months and intake should be limited to <500 mL daily in toddlers.
10. It is important to ensure that this dietary advice reaches high-risk groups such as socioeconomically disadvantaged families and immigrant families.

FUTURE RESEARCH DIRECTIONS

Future research directions are as follows:

1. There is a need for population-based studies of the prevalence of ID and IDA in young European children of different ages.
2. There is a lack of sufficiently powered randomized controlled studies of the effects of different levels of iron fortification in infant formula and follow-on formulas. Such trials are needed to better establish iron requirements in young children, based on effects on neurodevelopment, growth, and other health outcomes.
3. More studies are needed on the long-term health effects of different iron intakes in different risk groups.
4. Novel iron status indicators such as hepcidin and reticulocyte hemoglobin should be evaluated in children of different ages.

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