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Screening for Iron Deficiency Anemia in Childhood and Pregnancy: Update of the 1996 U.S. Preventive Services Task Force Review

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Abstract

Background. To update its 1996 guidelines, the U.S. Preventive Services Task Force (USPSTF) commissioned this brief update of the evidence on selected questions about screening for iron deficiency anemia (IDA) in children, adolescents, and pregnant women.

METHODS: We searched relevant databases, Web sites, journals, and reference lists for systematic reviews, epidemiologic surveys, and controlled trials published in 1995 or later that contained new information about the prevalence, diagnosis, natural course, or treatment of iron deficiency anemia in asymptomatic persons in developed countries. One investigator rated the quality of included trials and summarized their results in tables.

RESULTS: In the U.S., the average prevalence IDA in target groups is: Infants 1-2 years (6 to 17 per 1000), teenage girls (1.5%), nonpregnant females of reproductive age (2% to 5%). Factors associated with a higher prevalence include prematurity and low birth weight, black or Mexican-American race, Alaskan native heritage, recent immigration, poverty and, among teenage girls, fad dieting or obesity. The prevalence among pregnant women is not known.

For cognitive and school outcomes, trials of iron supplementation for iron deficiency anemia have had mixed results. Most trials conducted in high-risk groups within developed countries did not demonstrate any benefit for infants and preschool children, but one trial in high-risk infants demonstrated a transient benefit.

Introduction

Iron deficiency anemia has been associated with psychomotor and cognitive abnormalities and poor school performance in children, and with poor pregnancy outcome in pregnant women. In 1996, the U.S. Preventive Task Force (USPSTF) recommended one-time screening for iron deficiency anemia using hemoglobin or hematocrit for pregnant women and for high-risk infants, but not for other groups.¹ The Task Force recommended against routine testing for anemia in other children and in adults because of low prevalence, cost, and potential adverse effects of iron therapy.²

We undertook a limited review of recent literature to assist the USPSTF in updating its recommendations. This review was focused on key questions addressing gaps in the evidence that were identified in the USPSTF's 1996 review of screening for and treating iron deficiency anemia. Specifically, the critical key questions were:

- Is there direct evidence that screening for iron deficiency in asymptomatic children results in improved behavioral, motor, or cognitive development and/or growth?
- Does early iron supplementation in infants, children, adolescent girls, or pregnant women with iron deficiency anemia improve these outcomes?
- What are the adverse effects of screening for iron deficiency anemia?
- What are the adverse effects of iron supplementation?

For this review, we focused on studies conducted in developed countries that addressed one or more of these questions.

Background

Prevalence of Iron Deficiency and Iron Deficiency Anemia

Iron deficiency is the most common nutritional disorder worldwide. Severe or prolonged iron deficiency can cause iron deficiency anemia (IDA). The prevalence of IDA is sensitive to the age at testing and the diagnostic criteria used.

The hemoglobin concentration and hematocrit are the principal screening tests for detecting anemia. Hemoglobin can be measured quickly and accurately on a few drops of blood.³ Data on infants aged 6-12 months are sparse. For infants aged 1-2 years and 3-5 years, most studies use cut-offs for serum hemoglobin (Hgb) of <110 g/L and <112 g/L, respectively. Typical cut-off values for females are <118 g/L for 12- 14-year-olds and <120 g/L for 15- 39-year-olds.^{4,5}

These cut-off values were chosen by consensus or based on statistical analysis of the distribution of laboratory values in the population. Some experts argue that normal limits for Hgb and for iron studies should be based on analysis of the response to iron therapy, but efforts to define cut-off values in this manner have not yielded definitive results.⁶⁻⁸

Most cases of anemia are due to causes other than iron deficiency. When anemia is diagnosed, additional tests can determine whether iron deficiency is the cause. Centers for Disease Control and Prevention (CDC) analysts diagnose iron deficiency when two or more of the following tests are abnormal: free erythrocyte protoporphyrin ($\geq 1.24 \mu\text{mol/L}$ red blood cells), transferrin saturation (<14% for 12-15 year-olds or <15% for 16-39 year-olds), and serum ferritin (<12 $\mu\text{g/L}$).^{4,9}

While the CDC criteria are arbitrary, they have been used consistently across several analyses of the National Health and Nutrition Examination Survey (NHANES) (1988-1994 and 1999-2000), making comparisons across time and between demographic groups possible. Table 1 shows that the prevalence of IDA in infants aged 1-2 years (2% to 3%) and in females aged 12-19 years (2%) did not change substantively between these time periods.

Table 1. Prevalence of iron deficiency anemia in selected populations – United States, National Health and Nutrition Examination surveys, 1988-1994 and 1999-2000*

Sex / Age group (yrs)	1988-1994			1999-2000		
	No.	%	(95% CI) [†]	No.	%	(95% CI)
Both sexes						
1-2	1339	3	(2-4)	319	2 [‡]	(0-4)
Females[§]						
12-49	5982	4	(3-5)	1950	3	(2-4)
12-19	1486	2	(1-3)	1001	2	(1-3)
20-49	4495	5	(4-6)	949	4	(2-5)
50-69	2034	2	(1-3)	611	3 [‡]	(0.5-5)
≥ 70	1630	2	(1-3)	394	1 [‡]	(0-2)

Data from MMWR 2002.¹⁰

*All racial/ethnic groups.

[†]Confidence interval.

[‡]Unreliable; relative standard error (i.e., standard error/prevalence estimate) is > 30%.

[§]Non-pregnant only.

Not all studies use the CDC case definitions. The positive predictive value of a low hemoglobin for IDA varies with age and with the cut-off values used for case definition. Among children aged 12-35 months in NHANES III, the positive predictive value of Hgb concentration <110 g/L for iron deficiency was 29% (95% CI, 20–38%), and the sensitivity was 30% (95% CI, 20–40%). Changing the diagnostic cutoff point to

Hgb <107 g/L resulted in a positive predictive value of 38% (95% CI, 24–52%) but lowered the sensitivity to 15% (95% CI, 7–22%).⁸

Table 2 illustrates how the positive predictive value varies with age and with the cut-offs used to define IDA. In the Avon longitudinal study of pregnancy and childhood (ALSPAC), investigators developed criteria for the diagnosis of IDA based on the distributions of Hgb and ferritin levels in their own sample. By these (ALSPAC) criteria, 5% of infants 12 months or 18 months of age had a low Hgb value, and 10% or 12% of these infants, respectively, proved to have iron deficiency anemia. Using the World Health Organization (WHO) or Institute of Medicine (IOM) criteria, the apparent prevalence of anemia was between 17% and 18%, but the prevalence of IDA and the positive predictive value of a low Hgb value were much lower in infants 12 months of age than at 18 months of age.

Table 2. Percentage of infants with iron deficiency anemia at 12 and 18 months of age using different case definitions*

Criteria	Hgb Only		Hgb and Ferritin		Positive Predictive Value	
	12 months	18 months	12 months	18 months	12 months	18 months
ALSPAC criteria: Hgb < 100 g/l; Ferritin < 16 (age 12 mo.)/12 (18 mo.) µg/l	5%	5%	0.5%	0.6%	10%	12%
WHO: Hgb < 110 g/l; Ferritin < 12 µg/l	18%	17.3%	0.4%	1.7%	2%	9.8%
Institute of Medicine, USA: Hgb < 110 g/l; Ferritin < 10 µg/l	18%	17.3%	0.1%	1.1%	1%	6%

*Data From Sherriff et al¹¹

Hgb = Hemoglobin, IDA =Iron deficiency anemia

The prevalence of iron deficiency anemia among pregnant women is uncertain. Data from NHANES II suggest that <2% of nonpregnant women aged 20-44 years had IDA in the late 1970s.¹² The Pregnancy Nutritional Surveillance System (PNSS)

<http://www.cdc.gov/pednss/publications/index.htm>) has published annual rates of low Hgb or hematocrit (Hct) in a primarily low-income, pregnant U.S. program-based sample. These data indicate that the prevalence of anemia in the third trimester has not changed since the 1980s, but PNSS does not distinguish anemia related to iron deficiency from other causes. A surveillance program in Camden, New Jersey estimates that, in a low-income, mostly minority population, rates of IDA are 1.8% in the first trimester, 8.2% in the second trimester, and 27.4% in the third trimester.¹³

Risk factors for Iron Deficiency Anemia in Different Groups

Iron deficiency without anemia is a precursor to IDA. Factors that cause iron deficiency include inadequate iron intake or absorption, or increased iron requirements due to growth or to loss of iron from bleeding. Most people who have iron deficiency never develop anemia. However, if iron deficiency is severe or prolonged, depletion of iron stores can cause inadequate hemoglobin production and anemia.

The prevalence of IDA varies with age, sex, race, dietary intake, and socioeconomic factors. In the United States, the prevalence is higher among black and Mexican-Americans than among whites. Reliable estimates of rates of IDA in different subgroups are lacking, but good data on the prevalence of iron deficiency (with and without anemia) are available from NHANES. These data indicate that age-, race-, and gender-specific prevalences of iron deficiency in the U.S. population did not change substantially between 1990 and 2000 (see Appendix Table 1).¹⁰

As discussed below, other factors affect the risk of developing IDA in specific age and gender groups.

Risk factors among infants. The risk of iron deficiency anemia is high during the second year of life because of increased iron requirements related to rapid growth.^{11, 14-16} Premature and low birth weight infants and infants with history of prolonged stay in the neonatal unit are at particularly high risk of developing iron deficiency anemia before 1 year of age.¹⁷ Among term infants younger than 1 year, however, the prevalence of IDA is low, and Hgb and serum ferritin are uncorrelated.^{7, 18}

Risk factors for developing IDA in the second year of life include the use of non-iron-fortified formula in the first year of life (without therapeutic iron supplementation); exclusive breastfeeding with no or erratic iron supplementation after 6 months of age; and the introduction of cow's milk before 1 year of age.⁵ The prevalence of IDA increases between 12 and 18 months of age as these factors come into play.

At present, about 97% of formula sold in the United States is iron-fortified.¹⁹ Randomized and nonrandomized controlled trials, observational studies, and time series studies have demonstrated substantial reductions in the incidence of iron deficiency and IDA in healthy infants fed iron-fortified formula, iron-fortified cereal, or breast milk with iron-fortified cereal added at 4-6 months, compared with infants fed cow's milk or unfortified formula.

U.S. data on the impact of race, ethnicity, and socioeconomic factors on the risk of developing IDA in infancy are surprisingly sparse. The Pediatric Nutrition Surveillance System (PedNSS) measures hemoglobin levels in a national sample of infants from families participating in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), but does not perform iron-related measures. In the

2003 PedNSS report, the most recent to be published, 16.2% of infants aged 6-11 months had Hgb < 110 g/L, and 15% of children aged 12–17 months had Hgb < 110 g/L. The overall prevalence of anemia in PedNSS children declined from 15.8% in 1994 to 12.8% in 2003. The highest prevalence of anemia was among black infants (19.0%).²⁰ This survey establishes that black infants have a higher risk of anemia, but the proportion of cases that are related to iron deficiency is unknown.

In developing countries, and therefore among some groups of immigrants to North America, blood loss due to parasitic infection or malaria is a common cause of iron deficiency.²¹ Native American infants and recent immigrants from Cuba are also at risk for IDA. A study of First Nations communities in Canada determined the prevalence of anemia (defined as Hgb < 110 g/L) among 9-month-old infants to be 31.9%, and estimated that the prevalence of IDA to be 5.6% to 10.8%, based on Hgb < 110 g/L and a low mean cell volume as proxy measures for IDA.²² A 1998 Pan American Health Organization report estimated that IDA affects 40% to 50% of Cuban children aged 1-3 years.²³

Risk factors among adolescent girls and adult women. Females of childbearing age require additional iron. Heavy menstrual blood loss (≥ 80 mL/mo) and pregnancy are associated with higher iron requirements.^{5, 24}

Race, income, education, and other socioeconomic factors are associated with IDA in girls and women. In NHANES III, Mexican-American women aged 12-39 years were at higher risk of having IDA ($6.2\% \pm 0.8\%$) than non-Hispanic white women of the same age ($2.3\% \pm 0.4\%$), a difference that was marked among poor women but small for

women with higher household incomes (Table 3)⁹ and which could not be accounted for by differences in dietary intake of iron. We did not find an analysis of risk factors among black women.

Table 3. Prevalence of iron deficiency anemia in relation to poverty in Mexican-American and non-Hispanic white women aged 12-39 years

Poverty Income Ratio*	Mexican-American (n = 1194) % ± S.E.	Non-Hispanic white (n = 1183) % ± S.E.
≤1.3	6.9 ± 1.3	1.9 ± 0.8
>1.3–1.85	8.8 ± 2.2	4.9 ± 1.8
>1.85–3.0	4.4 ± 1.6	2.2 ± 0.8
>3.0	2.6 ± 0.9	1.9 ± 0.6 (not significant)

* Ratio of the total household income divided by the poverty threshold for the year of the interview. Data from NHANES III⁹

Eating disorders are also associated with IDA. An analysis of NHANES III data on 9698 children aged 2-16 years found that overweight and obesity were associated with a higher risk of IDA; in a logistic regression model controlling for age, gender, ethnicity, poverty status, and parental education level, children who were overweight were 2.3 times as likely to be iron-deficient (2.3; 95% CI, 1.4-3.9, respectively) as were those who were not overweight.²⁵ Adolescent girls who try to control their weight may inadvertently limit their iron intake. In Britain in the 1980s, the prevalence of IDA in adolescent girls was higher among girls who bought snacks at local shops instead of eating school lunches or bringing food from home.¹⁷

Complications of Iron Deficiency Anemia

As early as the 1960s, researchers demonstrated that, in general, decreased hemoglobin alone does not have readily apparent adverse effects unless it is below 10

g/dL (100 g/L).²⁶⁻²⁸ Persons with markedly reduced hemoglobin levels are at risk for cardiopulmonary and other complications. Screening is intended to find milder degrees of anemia before such complications have developed.

Infants and children. Several cross-sectional and case-control studies have demonstrated an association between IDA and psychomotor and cognitive abnormalities and poor school performance in children.^{17, 29-35} For example, in a recent cross-sectional analysis of NHANES III data, 71% of iron-deficient children had below-average math scores, versus 49% of children who had normal iron status.³⁴ Scores of tests on reading, block design, and digit span did not differ. After adjustment for age, gender, race, poverty status, caretaker education, and lead status, iron-deficient children were 2.4 times as likely to have low math scores (95% CI, 1.1-5.2; p=0.03). The effect was strongest among girls aged 12-16.

Several causal hypotheses have been proposed to explain this association. The oldest is that the brain functions poorly in IDA because of decreased oxygen delivery to tissues. According to this theory, correction of anemia could reverse the neurocognitive deficits seen in cross-sectional studies. An alternative hypothesis is that iron deficiency leads to increased absorption of lead, which can also cause brain damage.

Another alternative hypothesis is that, in the fetus, infant, and toddler, iron deficiency may cause abnormal metabolism of neurotransmitters or hypomyelination, leading to irreversible or very slowly reversible neurocognitive deficits. Evidence for this hypothesis comes primarily from animal studies.^{36, 37} Investigators seeking supporting evidence in humans have measured auditory brainstem responses and visual evoked potentials in a cohort of Chilean children who were diagnosed to have IDA as

infants. At the time of initial diagnosis at 6, 12, or 18 months of age, infants with IDA had slower transmission through the auditory brainstem pathway than healthy controls. Although IDA was diagnosed and treated early, at 4 years of age the children who had IDA as infants still had slower transmission than healthy infants.³⁸

A recent critical review identified seven longitudinal studies in which low hemoglobin levels in early childhood were linked to poor cognitive development or school achievement in later childhood.³⁵ (Two of these studies were available in 1996.) The older studies were small (range 20-41 anemic children) and the iron status of the anemic children was not clear.

One of the recent longitudinal studies using records from the WIC were linked to school records in Dade County, Florida.³⁹ The outcome variable for the analysis was mild or moderate mental retardation on the basis of criteria used by the Florida Department of Education for special education placement. About 69% of the sample (n=3,771) were black, 23% were Hispanic, and 7% were white. After adjustment for birth weight, maternal education, sex, race-ethnicity, age of mother, and age of child, there was a significant association between Hgb level at entry into the WIC program and the probability of mental retardation at age 10 (odds ratio 1.28; 95% CI, 1.05-1.60).

The other recent study⁴⁰ was a 10-year follow-up of a cohort of Costa Rican children, the subject of previous reports in infancy and at 5 years of age. In this cohort, 48 children who had severe iron deficiency in infancy were compared with 114 children who had good iron status in infancy. At ages 11-14 years, the children who had severe iron deficiency as infants still had worse scores on intelligence tests (101.8 ± 2.0 vs. 104.6 ± 1.3) and on a variety of tests of cognitive function, despite having similar Hgb

levels in adolescence. Parents of children in the severe iron deficiency group were more likely to report behavior problems.

It is difficult to prove that the relationship between anemia and developmental abnormalities in longitudinal studies is causal. Many other factors associated with abnormal neurocognitive development are also associated with iron deficiency. These include nutritional factors, such as intake of iodine, zinc, and other micronutrients; environmental factors (e.g., exposure to lead); prematurity and low birth weight; caretaker characteristics (e.g., maternal education, household income); and other socioeconomic factors.^{35, 41} In all cross-sectional studies, iron-deficient children and their families differed in nutritional status, income, education, and other factors from the comparison groups.³⁵ Most longitudinal studies did not include enough children to control for all environmental variables that could be associated with iron deficiency and with the outcomes.³⁵

Socioeconomic factors are so strongly associated with cognitive outcomes, and so highly inter-correlated, that the ability of statistical adjustment to eliminate confounding is uncertain. In the Dade County study, for example, maternal education was a powerful predictor of mental retardation after adjustment for other risk factors. Compared with maternal education greater than 12 years, the adjusted odds associated with only 12 years of maternal education and less than 12 years were 8.32 (95% CI, 1.12-62.0) and 11.9 (95% CI, 1.63-88.1), respectively. In the Costa Rican study, maternal IQ and education were strongly associated with children's IQ and with cognitive abnormalities.

Screening is most likely to influence neurodevelopmental outcomes if it is done at an age when IDA is present and development is still normal.¹⁴ Investigators from the

AVON longitudinal study of pregnancy and childhood sought to identify the best age for screening by examining the relationship between serum Hgb and developmental outcomes, measured at age 18 months.^{11, 14} Delayed development by age 18 months was associated with anemia at 8 months of age. However, most abnormalities that would lead to a diagnosis of iron deficiency without anemia resolved spontaneously by 12 or 18 months of age.

Pregnancy. Numerous observational studies have reported an association between severe to moderate anemia (hemoglobin <9–10 g/dL) and poor pregnancy outcome.² However, the relationship between maternal iron deficiency or IDA during pregnancy and birth outcome is not well understood. Older studies, including three large, population-based studies, evaluated the relationship between Hgb or Hct and low birth weight or premature birth without assessing the iron status of the mother. Recent cohort studies⁴² and reviews,^{13, 43} including a critical review of studies published between 1966 and 1999,⁴⁴ emphasize that the relationship of maternal Hgb to birth weight is U-shaped—that is, low and high Hgb values are markers for poor birth outcomes. In white women, maternal hemoglobin values of 105–125 g/L were associated with the lowest rate of LBW. For black women, the rate of low birth weight was lowest for maternal hemoglobin values of 85–95 g/L, but this estimate is based on data that are now over 25 years old. In the first trimester, IDA is associated with a greater than two-fold increase in the risk of preterm delivery. In the third trimester, however, lower Hgb and Hct levels are not associated with higher rates of low birth weight or preterm delivery.

Maternal IDA might have other complications. One prospective, longitudinal human study found an association between low umbilical cord serum ferritin concentrations and poor performance on mental and psychomotor tests at 5 years of age.⁴⁵ Low postpartum Hgb or Hct levels may be associated with postpartum depression.⁴⁶

Postpartum maternal IDA may also be associated with developmental delay in children. A controlled trial of iron therapy in young, South African mothers with IDA, published in 2005, compared non-anemic mothers with anemic mothers administered either placebo (25 mg ascorbic acid and 10 µg folate) or daily iron treatment (125 mg FeSO₄) plus ascorbate and folate).⁴⁷ All mothers had full-term, normal birth weight infants (n = 81) and were enrolled in the study at 6-8 weeks postpartum. At baseline, anemic mothers tended to be less responsive to, and more controlling of, their infants than non-anemic mothers. Infants of anemic mothers were delayed at 10 weeks in hand-eye movement and overall development. Infants whose mothers were anemic in the early postpartum period scored worse on developmental tests at 10 weeks and 9 months of age. At 9 months, anemic mothers in the placebo group were significantly more negative toward their babies, engaged less in goal setting, and were less responsive than non-anemic mothers in the control group.

Methods

Problem Formulation

Members of the USPSTF defined the scope of this update with input from Agency for Healthcare Research and Quality (AHRQ) and Evidence-based Practice Center (EPC) personnel.

Search for New Studies

The search was focused on the following key questions:

- Is there direct evidence that screening for iron deficiency in asymptomatic children aged 6-12 months results in improved health outcomes; that is, abnormal infant behavior, growth, and development (longer-term outcomes)?
- Is there evidence that early iron supplementation in infants, children, adolescent girls, or pregnant women with iron deficiency anemia improves these outcomes?
- What are the adverse effects of screening for iron deficiency anemia?
- What are the adverse effects of iron supplementation?

EPC personnel searched the Cochrane Database of Systematic Reviews (2005, v.2), Cochrane CENTRAL (2005, v.2), reference lists of review articles, and tables of contents of leading pediatric journals for studies published 1995 or later that contained new information about the prevalence, diagnosis, natural course, or treatment of iron deficiency anemia in asymptomatic persons. We also searched the web site of the *Iron Deficiency Project Advisory Service* Working Group on Iron Deficiency Anemia in Children < 2 (<http://www.micronutrient.org/idpas/WorkingGroup.html>), which

maintains bibliographies and reprints of articles about the prevalence and cognitive consequences of iron deficiency in developing countries.

Articles that met the following criteria were included in this update:

- 1) The study was a systematic review, prospective cohort study, controlled trial, quasi-experimental study with concurrent controls, or case-control study; not a case series, case report, or comparison with historical controls.
- 2) The study was not included in the 1996 review.
- 3) The study was rated at least “fair-quality” using the USPSTF criteria for internal validity.⁴⁸

Synthesis

Eligible studies were rated and abstracted by one investigator. Because several recent meta-analyses were available, the investigator did not conduct a new quantitative synthesis; instead the focus was on reporting the results of a critical appraisal of trials published since the USPSTF’s 1996 guideline. USPSTF members also reviewed key studies identified in the review.

Results

Is there direct evidence that screening for iron deficiency anemia in asymptomatic children aged 6-12 months results in improved health outcomes; that is, abnormal infant behavior, growth, development (longer-term outcomes)?

We did not find any controlled trials of screening for IDA. In the United States, an uncontrolled, practice-based study conducted at the pediatric resident clinic at Johns Hopkins University described the results of an effort to implement the screening strategy recommended by the American Academy of Pediatrics.⁴⁹ Of 1358 clinic patients aged 9-36 months who were screened, 343 (25%) had an Hgb level less than 110 g/L. About half of these infants had mild anemia (Hgb 106 to 109 g/L). Of these, 75 were prescribed iron and anemia resolved by 6 months of follow-up in 55 (73%). Another 25 were not prescribed iron, and anemia resolved by 6 months in 21 (84%). For those who had Hgb levels <106 g/L, 61 of 90 (68%) treated children resolved by 6 months, versus 6 of 15 (40%) untreated children.

Is there evidence that early iron supplementation in infants, children, adolescent girls, or pregnant women with iron deficiency anemia improves outcomes?

Infants and children. Improved growth and weight gain with 3-6 months of iron supplementation have been reported consistently in placebo-controlled trials of anemic, malnourished children in developing countries.

Whether treatment is also associated with improvements in cognition, behavior, and motor development is less clear. The U.S. Preventive Services Task Force, in 1996, noted that trials of treatment of infants with IDA to improve neurodevelopmental outcomes had conflicting results. Some of the trials reporting a benefit had serious flaws.^{50, 51} A Cochrane review, published in 2001, found seven trials of treatment in

children up to 3 years of age; all these trials were published prior to 1994 and had been cited in the Task Force's review (Table 4).⁵² The Cochrane review concluded that there was a lack of clear evidence of a beneficial effect on psychomotor development.

A review by Grantham-McGregor and colleagues included trials as well as observational studies.³⁵ With the exception of one trial published in 1993,⁵³ short-term and longer-term trials found no benefit of iron supplementation on intelligence tests, tests of cognitive function, or other neurodevelopmental outcomes, and the observational studies had not adequately addressed potential confounders.

Table 4. Neurodevelopmental outcomes in children under age 3 with iron deficiency anemia (articles included in Cochrane Review and 1996 USPSTF reviews)

Trial (Funding Source)	Setting	Subjects	Age (mos.)	N	Design Characteristics	Treatment (duration)	Control	Follow-up Assessment	Time	Results
Oski and Honig, 1978 ⁵⁴	Pediatric Clinic in New York	IDA (Hgb<10.5 g/dl)	9-29	24	DBRCT. No details of allocation process available.	IM iron dextran complex once.	Placebo of IM sterile saline once.	BSID, BIB.	1 wk.	Improved alertness, gross and fine motor coordination.
Lozoff, 1982 ⁵⁵	Community volunteers, Guatemala	IDA (Hgb<10.5 g/dl)	6-24	28	DBRCT. Allocation by investigators not connected with study.	Oral iron for 7 days.	Placebo.	BSID.	6 -8 days	NS trend in PDI, no difference in MDI.
Lozoff, 1987 ²⁹	-	Anemia (Hgb<=10.5g/dl)	-	52	DBRCT. Allocation by investigators not connected with study.	IM or oral iron for 7 days.	Placebo.	BSID.	7 days	No difference.
Walter, 1989 ³³	Community sample, Chile	IDA (Hgb<10.5g/dl)	12	39	Unclear. Method of allocation unclear.	Ferrous sulphate 45 mg day for 10 days.	Placebo.	BSID.	3 mos.	No difference.
Kimmons, <i>un-published</i>	General pediatric clinic, U.K.	IDA (Hgb<10.6g/dl, MCV<73)	6 -24	42	DBRCT. Allocation by nurse not connected with study.	IM Iron dextran complex.	Placebo.	BSID.	1 wk.	No difference.
Aukett, 1986 ⁵⁶	Community Sample	IDA (Hgb 8-11g/dl)	17-19	110	DBRCT. Allocation by investigators not connected with study.	Oral iron plus vitamin C.	Placebo.	DDST, weight change.	8-9 wks.	No difference.
Idjradinata, 1993 ⁵³	Pediatric clinic in Indonesia	IDA (Hgb<=10.5g/dl)	12-18	50	DBRCT.	Oral iron for 4 months.	Placebo.	BSID, weight, length.	4 mos.	PDI + 18.4 MDI + 18.8

BSID = Bayley Scales of Infant Development, DBRCT= Double-blinded randomized controlled trial, DDST = Denver Development Screening Test, Hgb = Hemoglobin, IDA = Iron deficiency anemia, IM= Intramuscular, MCV = Mean corpuscular volume, MDI = Mental Development Index, NS = Not significant, PDI = Psychomotor Development Index, USPSTF = U.S. Preventive Services Task Force

The conflicting results in trials of treatment for IDA have called into question the reversibility of neurodevelopmental abnormalities associated with IDA, and have led to increased interest in preventing rather than remediating iron deficiency. Until recently, few trials of primary prevention examined neurocognitive or behavioral endpoints. Moreover, as many studies do not distinguish between high-risk subjects who have IDA and those who have iron deficiency without anemia, it is very difficult to distinguish the effect of prophylactic iron supplementation from the effect of treatment of existing iron deficiency.

A recent meta-analysis⁵⁷ combined 17 trials of iron supplementation in infants or in children up to 12 years of age. Sixteen trials were published 2001 or earlier and one was unpublished. Ten of the trials were conducted in developing countries, two were from the United States,^{31, 58} two were from the United Kingdom,^{56, 59} one was from Canada,⁶⁰ and one was from Greece.⁶¹ The main measure was the “mental development score,” derived by combining any available scores from the Bayley Mental Development Index (MDI), Stanford Binet Test, Peabody Picture Vocabulary Test (PPVT), IQ, and cognition tests. Overall, the standard mean difference in mental development scores was 0.30 (95% CI, 0.15 to 0.46, $p < 0.001$), a difference equivalent to equivalent to 1.5 to 2 points on a scale of 100. Separate analyses for mental development tests and motor development found no statistically significant differences.

The trials pooled in this meta-analysis included diverse subjects, settings, clinical interventions, and outcome measures. Because of this heterogeneity, the overall pooled result has little or no applicability to the United States. In subgroup analyses, the improvement in mental development scores was attributable to five trials in children aged 7 years and older (standard mean difference,

0.44; 94% CI, 0.21-0.66, $p < 0.0001$) conducted in India (2), Thailand (1), and Indonesia (2). The effect was small and statistically not significant for infants under 2 years of age (0.15, CI 0.04-0.34, $p = 0.128$). The effect is intermediate for children between 2 and 5 years of age.⁶² More recent trials in developing countries have had mixed results (Table 5 and Evidence Table 1, Panel 1).⁶³⁻⁶⁵

Table 5. Recent trials of iron supplementation on cognitive or motor development in developing countries

Trial / Design	Subjects / Setting	Results
Lozoff, 2003 ⁶³ Partly randomized	1657 infants 6 or fewer months old Chile	Bayley Scales and Fagan test of Infant Intelligence at 12 months. No difference in PDI or MDI scores at 12 months. On Fagan test, mean looking time was longer in the no-iron-added group (1.39 ± 0.02 seconds vs. 1.46 ± 0.04).
Lind, 2004 ⁶⁴ RCT	680 full-term infants aged 6 months Indonesia	Bayley Scores at 12 months. PDI in Iron group 106 ± 11 vs. placebo group 103 ± 10.8 . MDI in Iron group 101 ± 9.3 vs. placebo group 99 ± 10 . No difference in Behavioral Rating Scale.

MDI = Mental Development Index, PDI = Psychomotor Development Index, RCT = Randomized controlled trial

In their review, Grantham-McGregor³⁵ and colleagues identified three prevention trials conducted in developed countries^{59, 60},⁶⁶ that measured motor, cognitive, or behavioral function. One⁶⁰ of these, conducted in Canada, was reviewed by the USPSTF previously. In this trial, infants from very low-income families were randomized to take iron-fortified versus unfortified formula.

Those who were fed iron-fortified formula had significantly higher Bayley motor scores at 9 and 12 months. By 18 months there was no longer any effect, but by that time 46% of the subjects had been lost to follow-up.

Trials conducted in developed countries and published since the last USPSTF review are summarized in Table 6 (see Evidence Table 1, Panel 2 for more details). Two trials (which were included in the review by Grantham-McGregor and colleagues) evaluated iron-fortified formula in low socioeconomic status areas of the United Kingdom.^{59, 66} We also identified a Canadian trial of iron supplementation in infants 1 to 6 months of age⁶⁷ and one of preschoolers conducted in nine day care centers in Athens, Greece,⁶⁸ neither of which has been included in previous systematic reviews.

Table 6. Effect of iron supplementation on infants in developed countries

Trial / Design	Subjects / Setting	Results
<i>Developed countries</i>		
Williams, 1999 ⁶⁶ RCT	100 full-term infants aged 6-8 months Low-income England	Griffith's scale at 18 and 24 months. No differences at 18 months. At 24 months, global developmental quotient fell 5.4 points more in the non-fortified group than in the fortified group ($P<0.05$).
Morley, 1999 ⁵⁹ RCT	493 full-term infants aged 9 months. England	MDI and PDI at 18 months. No differences.

Trial / Design	Subjects / Setting	Results
Friel, 2003 ⁶⁷ RCT	77 full-term infants aged 1 month Canada	MDI, PDI and vision at 13 months. PDI scores were higher in the iron supplemented group (100 ± 12 vs. 93 ± 9 ; normal range 85 to 115). MDI scores did not differ. A trend ($P = .07$) was observed toward improved visual acuity with iron.
Metallinos-Katsaras, 2004 ⁶⁸ RCT	49 3- 4-year olds (21 anemic, 28 good iron status) Greece	Small improvement in discrimination, specifically selective attention in anemic children, but not others.

MDI = Mental Development Index, PDI = Psychomotor Development Index , RCT = Randomized controlled trial

Adolescent girls. An older trial (1986) of pregnant young women found better performance on psychometric tests in women treated with iron than in controls.⁶⁹ A more recent placebo-controlled trial (published in 1996), conducted in two public and two private Catholic high schools in Baltimore, Maryland in 1993, examined the effects of iron supplementation on cognitive function in nonanemic, iron-deficient adolescent girls.⁷⁰ Of 716 girls in grades 9–12 (aged 13–18) screened, 35 were found to have anemia (Hgb < 11.5 g/dL for African American girls or < 12.0 g/dL for white girls) and 98 had iron deficiency without anemia. Eighty-one of these 98 girls agreed to participate in a randomized trial and 73 of them completed the 8-week follow-up period. Girls randomized to treatment took two 325 mg tablets of nonprescription ferrous sulfate twice daily (260 mg elemental iron daily.) Four cognitive tests were administered at baseline and after 8 weeks of treatment. Although more girls in the treatment group than in the placebo group

noticed changes in stool color (65% v 10%, $p < 0.001$), the percentage of girls who correctly guessed their group assignment did not differ significantly between groups (62% in treatment compared with 45% of controls, $p = 0.18$).

The four tests were the Symbol Digit Modalities Test (SDMT); Visual Search and Attention Test (VSAT); Brief Test of Attention (BTA); and the Hopkins Verbal Learning Test (HVLT). Only subjects who completed the study were included in the analysis. Treatment had no effect on the SDMT, VSAT, or BTA, all of which are considered to be tests of attention. The authors described the other test, HVLT, as follows:

“The HVLT is a 12-item, semantically categorized word-list learning test with three free recall trials, a delayed recall trial, and yes/no recognition; participants are read the same list of words three times and each time are asked to repeat as many words as they can recall; 20 minutes later they are asked to say which words they remember, and are read 24 words which include the original 12 words plus 12 semantically related and unrelated words.”⁷⁰

By the author’s description, the HVLT, which is considered a test of learning, is scored in three parts—the sum of the three recall trials (the “total recall score”), the delayed recall trial, and the recognition part. The article reported an average baseline HVLT total recall score for the treatment and placebo groups, but did not report the post-treatment scores. The authors state that “on the total recall score of the HVLT (sum of trials 1–3), girls who took iron showed significant improvement over baseline and end of treatment

compared with the control group ($p < 0.02$). Baseline performance on the HVLТ accounted for 93% of the variability in post-intervention scores, whereas treatment condition accounted for the remainder. However, there were no significant differences between groups in other components of the HVLТ (delayed recall, yes/no recognition).” From the published results, it is impossible to determine the magnitude of effect or how many girls’ scores improved, stayed the same, or worsened in each group.

Pregnant women. A large body of data suggests that iron supplements are effective in improving the hematologic indices of pregnant women, but there is limited evidence that improving hematologic indices in anemic women results in improved clinical outcomes for the mother, fetus, or newborn. Clinical trials have reported that iron supplements in healthy pregnant women with initial hemoglobins ≥ 10 g/dL are efficacious in correcting red cell indices and iron stores, but they do not improve birth weight, length of gestation, or other outcome measures when compared with placebo or with no supplements.⁷¹⁻⁷⁷ A 2005 review of community-based interventions to improve perinatal and maternal outcomes in developing countries also found no clear evidence that iron supplementation improved maternal and perinatal or neonatal outcomes.²¹

A Cochrane review found that iron supplementation appears to prevent low hemoglobin at birth or at 6 weeks postpartum, but concluded there were no reliable data from controlled trials about the pregnancy outcomes for either mother or baby.⁷⁸ The largest trial included in the Cochrane review compared selective versus routine supplementation in 2693 pregnant Finnish women.⁷⁹ The initial results of this trial showed a statistically significant increased likelihood of cesarean section (OR 1.36; 95% CI, 1.04 -1.78) and of

post-partum blood transfusion (OR 1.68; 95% CI, 1.05 -2.67) in the selective supplementation group compared with routine supplementation. The authors attributed the increased cesarean sections and blood transfusion rates to possible anxiety by midwives and obstetricians about low hematocrit values in the selectively supplemented group. Selective supplementation was associated with a significantly reduced risk of stillbirth after 28 weeks' gestation and of death in the first 7 days after birth. There were also fewer women in this group who complained of side effects from the medication. In a 7-year follow-up study, fewer infants in the selective supplementation group had been hospitalized for convulsions (OR 0.44; 95% CI, 0.25-0.79).⁸⁰

The Cochrane review did not include an American trial published in 2003 of iron supplementation in 275 low-income pregnant women who had a hemoglobin concentration >110 g/L and a ferritin concentration >20 g/L.⁸¹ The women were enrolled before 20 weeks of gestation and randomly assigned to receive a monthly supply of capsules containing either 30 mg iron as ferrous sulfate or placebo until 28 weeks of gestation. For unclear reasons, women assigned to the placebo group had higher baseline pre-pregnancy weight ($77.9\text{kg} \pm 24.3$ vs. $72.5\text{kg} \pm 20.3$, $p=0.04$) and initial ferritin levels ($49.4\mu\text{g/L}$ vs. $44.7\mu\text{g/L}$, $p=0.0168$). Of these 275 women, 62 were excluded from the analysis because the investigators could not obtain birth weights. For the 213 newborns included in the analysis, birth weight $< 2,500$ grams occurred less frequently in the iron supplementation group (4.3% vs. 16.7%, $p=0.003$), though the risk of preterm delivery was not different (12.8% vs. 12.5%.)

What are the adverse effects of screening for iron deficiency anemia?

We did not identify any studies of the harms of screening for IDA.

What are the adverse effects of iron supplementation?

Many infants dislike the taste of oral iron preparations or have gastrointestinal side effects. The likelihood of response to treatment for iron deficiency anemia identified by screening is unclear because so many families or infants do not accept treatment and because the rate of spontaneous resolution is high. In the population-based Millennium Baby Study cohort from Glasgow, UK, for example, 147 children aged 13 months were offered treatment because they had a low Hgb, ferritin, MCV, MCH, or high protoporphyrin level.⁷ Of these, 124 families accepted the first bottle of oral iron, but only 83 accepted a second bottle 3 weeks later. Thirty-one families reported that iron had caused diarrhea and many infants refused to go back on iron-fortified formula milk. A practice-based UK general practitioner study noted similar problems.⁸²

Many controlled trials of iron have examined whether new forms of iron replacement, combinations of micronutrients, and iron regimens requiring less frequent dosing can improve compliance and iron status in infants,⁸³⁻⁹² preschool children,^{93, 94} school children (including adolescents),⁹⁵⁻¹⁰⁰ and pregnant women.^{101, 102}

Adverse effects of iron therapy include unpleasant gastrointestinal symptoms (e.g., nausea and constipation) that are dose-related and, at normal doses, reversible. Iron therapy can cause complications of excessive iron storage in patients with an underlying iron storage disorder (e.g., idiopathic hemochromatosis).^{103, 104} A potential hazard of iron supplements is unintentional overdose by

children in the home. Iron overdose is a concern because it has been observed even in the context of controlled trials and screening programs in which parents were instructed in the safe storage and use of iron-containing products.

Iron supplements accounted for 30% of fatal pediatric pharmaceutical overdoses occurring between 1983 and 1990.¹⁰⁵ In 1997, to reduce the danger of overdosage, the U.S. Food and Drug Administration (FDA) required unit-dose packaging for iron-containing dietary supplement and drug products that contain 30 milligrams (mg) or more of iron per dosage unit.¹⁰⁶ According to an analysis of American Association of Poison Control Center Toxic Substance Surveillance System (AAPCCTSSS) abstracts, the regulations were associated with a reduction in deaths of children from iron ingestions. From 1983 through 2000, a review of the AAPCCTSSS system showed that at least 43 children had died from the ingestion of iron supplements, but only one child was reported to have died from the ingestion of an iron-containing product from 1998 through 2002 while the regulation was in effect.¹⁰⁷

In October 2003, the FDA withdrew this requirement in response to a court ruling in the case of Nutritional Health Alliance versus FDA, in which the Court concluded that the Federal Food, Drug, and Cosmetic Act does not provide the FDA with authority to require manufacturers of iron-containing dietary supplement and drug products to use unit-dose packaging for poison prevention purposes.¹⁰⁸ All iron-containing supplements must carry the warning “Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6.”

Other potential adverse effects of iron mentioned in the literature (e.g., birth defects, cancer, heart disease, metabolic imbalances of other minerals, and harmfully high hemoglobin levels) have not been proven. A recent meta-analysis of 28 placebo-

controlled trials of iron supplements in 7,892 infants and children found no increased risk of infection (1.02 [95% CI, 0.96-1.08]) and an 11% increase in the risk of diarrhea corresponding to one episode per 20 children per year (95% CI, 1.01-1.23; P=0.04).¹⁰⁹

Recommendations of Other Groups

In 1998, the Centers for Disease Control and Prevention (CDC) published recommendations to prevent and control iron deficiency.⁵ In addition to pregnant women and high-risk infants, the CDC recommended screening among high-risk preschool children and among nonpregnant women of childbearing age. The CDC also recommended “universal iron supplementation to meet the iron requirements of pregnancy.”

The American Academy of Pediatrics (AAP) recommends checking hemoglobin (or hematocrit) between 9 and 12 months of age and then 6 months later, and, for patients at high risk, once a year from age 2 to 5 years. Screening may be universal or selective depending on the prevalence of IDA in the local or demographic population. The AAP also recommends that adolescent girls be screened for anemia during all routine physical examinations.¹⁶

The 2005 AAP breastfeeding guidelines recommend continuing breastfeeding for at least the first year of life and beyond, while introducing complementary foods rich in iron beginning around 6 months of age. Preterm and low birth weight infants and infants with hematologic disorders, or infants who had inadequate iron stores at birth, generally require iron supplementation before 6

months of age. The AAP recommends that infants weaned before 12 months of age receive iron-fortified infant formula instead of cow's milk.¹¹⁰

The American Academy of Family Physicians (AAFP) recommends screening for IDA by obtaining hemoglobin and/or hematocrit levels in infants aged 6 to 12 months who are living in poverty, or who are black, Native American, or Alaska Native, immigrants from developing countries, preterm and low birth weight infants, and infants whose principal dietary intake is unfortified cow's milk.

The American College of Obstetricians and Gynecologists (ACOG) recommends prenatal screening for all women at the earliest prenatal visit and early in the third trimester. Screening of older children or nonpregnant adolescents and adults is not recommended.

The Veterans Administration/Department of Defense guideline panel found insufficient evidence to recommend for or against routinely supplementing iron for all pregnant women who are not anemic. They recommended supplementation with at least 50 mg elemental iron (325 mg ferrous sulfate) twice a day in all pregnant women diagnosed with anemia (hematocrit <30).

Summary and Discussion

Iron deficiency anemia is a serious problem worldwide. Although it is less common in developed countries such as the United States and Canada, where the use of iron supplemented formula is widespread, within these countries it is still a major concern among vulnerable populations, particularly in recent immigrants, native Americans, and poor African-American communities.

While iron deficiency anemia in infancy is a marker for poor neurocognitive development subsequently, screening and early treatment have not consistently improved these outcomes. Two leading hypotheses have been advanced to explain these disappointing results. One is that prevention of neurodevelopmental consequences of iron deficiency anemia may require acting to prevent iron deficiency in the first place rather than detection and treatment of existing iron deficiency. At present there is little evidence to support this hypothesis, but additional studies, particularly in developing countries, may confirm it. The second hypothesis is that prevention of neurodevelopmental consequences may require screening and early treatment of multiple nutritional deficiencies, rather than iron deficiency anemia alone.

In adolescent girls, a few provocative studies indicate that early detection or prevention of iron deficiency might improve social adjustment and cognitive function. In pregnant women, there are no reliable data from controlled trials about the pregnancy outcomes for either mother or baby.⁷⁸

Table 7 summarizes the main findings of this update.

Table 7. Summary of the evidence

Question	Group(s)	Findings	Comments
What is the burden of illness of iron deficiency anemia in the U.S.?	All	Overall, prevalence now and in the mid-1990s is similar. Prevalence in the groups targeted for screening are: <i>Infants 1- 2 years (7%), teenage girls (9%), non-pregnant females of reproductive age (12%).</i>	-
Prevalence	All	Estimated prevalence in the groups targeted for screening are: <i>Infants 1-2 years (6 to 17 per 1000), teenage girls (1.5%), non-pregnant females of reproductive age (2% to 5%).</i> The prevalence among pregnant women is uncertain.	-
Risk Factors	All	Risk factors include female sex, black or Mexican-American race, Alaskan native heritage, recent immigration, poverty, and among teenage girls, fad dieting or obesity. Premature and low birth weight infants are at high risk.	-
Complications	Infants and children	In cross-sectional and longitudinal cohort studies, iron deficiency anemia as an infant is associated with long-term psychomotor and cognitive abnormalities, poor school performance, and mental retardation. However, confounding due to environmental, socioeconomic, and other nutritional factors cannot be excluded.	-
	Pregnant women	Low or high hemoglobin values in the first trimester are associated with an increased risk of premature birth. Maternal anemia may be associated with poorer parental interaction and poorer developmental outcomes at 9 months of age.	-
	All	Severe iron deficiency anemia is symptomatic (fatigue, reduced endurance) and reduces work productivity.	-
Is there direct evidence that screening for iron deficiency anemia results in improved health outcomes?	Infants and children	<i>(Poor.)</i> In controlled trials and time-series studies, screening and treatment for iron deficiency anemia can reduce the prevalence of iron deficiency anemia in high-risk populations, but there are no data that directly link screening with better neurodevelopmental outcomes.	-

Question	Group(s)	Findings	Comments
Does early iron supplementation in people with (or at risk for) iron deficiency anemia improve neurodevelopmental outcomes?	Infants and children	<i>(Fair.)</i> The results of trials are mixed. Most trials conducted in high-risk groups within developed countries did not demonstrate any benefit for infants and preschool children, but in one trial in high-risk infants there was a transient benefit.	-
	Older children	<i>(Fair.)</i> Iron supplementation for infants aged 3-6 months improves growth and weight gain in anemic, malnourished children aged 7-10 years in developing countries. There is no evidence directly relevant to screening in the U.S.	-
	Adolescent girls	<i>(Poor.)</i> In girls who had iron deficiency but not iron deficiency anemia, iron supplementation improved performance on tests of verbal learning, but the magnitude or duration of the benefit was not clear.	-
	Pregnant girls and women (effect on the mother)	<i>(Poor.)</i> In one small trial conducted in Baltimore in the early 1980s, supplementation improved short-term memory and attention span. In a South African trial, treatment of anemic mothers enrolled at 6-8 weeks postpartum improved parenting (Parent/Caregiver Involvement Scale) assessed at 9 months.	-
	Pregnant girls and women (effect on the child)	<i>(Fair.)</i> Most studies of treatment found no effect on birth outcome. The most recent trial found a substantial increase in birth weight, but had important flaws.	-
What are the adverse effects of screening for iron deficiency anemia?	Infants and children	No evidence.	Potential harms: cost, time, anxiety, false-positives

Question	Group(s)	Findings	Comments
What are the adverse effects of iron supplementation?	Infants and children	<i>(Good.)</i> Accidental overdose is the most serious potential adverse event. Diarrhea is a common side effect (incidence rate difference 0.05 episodes/child year, -0.03 to 0.13; P=0.21). Cohort studies have reported no important adverse effects with iron-fortified formula, nor were serious side effects reported in the clinical trials of iron-fortified food or formula.	No new evidence of additional harms. There is good evidence that overdose of iron can cause fatal poisoning.
	Pregnant women	<i>(Poor.)</i> In one Finnish trial of pregnant women, routine iron supplementation led to a higher cesarean section rate, but this result has not been verified.	-

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Appendix Table 1. Prevalence of Iron Deficiency - United States, National Health and Nutrition Examination surveys, 1988-1994 and 1999-2000*

Sex/Age group (yrs)	1988-1994			1999-2000		
	No.	%	(95% CI) [†]	No.	%	(95% CI)
Both Sexes						
1-2	1339	9	(6-11)	319	7	(3-11)
3-5	2334	3	(2-4)	363	5	(2-7)
6-11	2813	2	(1-3)	882	4	(1-7)
Males						
12-15	691	1 ^{‡§}	(0.1-2)	547	5 [§]	(2-8)
16-69	6635	1 [§]	(0.6-1)	2084	2 [§]	(1-3)
70	1437	4	(2-3)	381	3 [‡]	(2-7)
Females 						
12-49	5982	11	(10-12)	1950	12	(10-14)
12-15	786	9	(6-12)	535	9	(5-12)
16-69	700	11	(7-14)	466	16	(10-22)
20-49	4495	11	(10-13)	949	12	(10-16)
White, non-Hispanic	1827	8	(7-9)	573	10	(7-13)
Black, non-Hispanic	2021	15	(13-17)	498	19	(14-24)
Mexican American	1845	19	(17-21)	709	22	(17-27)
50-69	2034	5 [§]	(4-7)	611	9 [§]	(5-12)
70	1630	7	(5-8)	394	6	(4-9)

Data from MMWR 2002.¹⁰

*All racial/ethnic groups except where noted.

[†]Confidence interval.

[‡]Unreliable; relative standard error (i.e., standard error/prevalence estimate) is > 30%.

[§]P<0.05 for comparison between surveys within age and sex category.

|| Non-pregnant only.

Evidence Table 1. Iron supplementation trials

Panel 1. Supplementation in developing countries										
Trial	Setting	Subjects	Age (mos.)	N	Design Characteristics	Treatment (duration)	Control	Follow-up Assessment	Time (mos.)	Results
Lozoff, 2003 ⁶³ (Formula donated by maker)	Four working-class communities on the outskirts of Santiago, Chile	Breastfed infants, weaned after 6 months.	6	1657	Partly randomized. Blinding unclear. Some baseline differences in compared groups. Outcome assessment was incomplete.	High-iron formula (12 mg/L) or low-iron formula (2.3 mg/L)	No-iron-added cow's milk plus multivitamin without iron (n=584)	BSIS, Fagan Test of Infant Intelligence.	12	No difference in PDI or MDI scores. Longer looking time in controls (1.39±0.02 seconds vs. 1.46±0.04 s)
Lind, 2004 ⁶⁴ (Industry)	Purworejo, Central Java, Indonesia (malnutrition)	680 healthy term infants.	6	680	Randomized. Probably blinded. 655/680 analyzed.	Iron or Zinc plus Iron.	Zinc alone or placebo.	BSIS.	12	PDI 106 ± 11 vs. placebo group 103 ± 10.8.
Panel 2. Supplementation in developed countries										
Trial	Setting	Subjects	Age (mos.)	N	Design Characteristics	Treatment (duration)	Control	Follow-up Assessment	Time (mos.)	Results
Moffatt, 1994 ⁶⁰	Low-income, high-risk urban hospital clinic, Canada	Healthy infants	<6	283	DBRCT. High dropout rate. 20.5% dropped out before any outcome data were gathered; 225, 204, 186, and 154 remained at 6-, 9-, 12-, and 15-month assessments.	Iron-fortified formula.	Regular formula.	BSID.	15	Better psychomotor scores (+6.4) at 9 and 12 months but not at 15 months; no differences in cognition or behavior.
Williams, 1999 ⁶⁶	Low-income, high-risk area neighborhood clinic, Birmingham, England.	Term infants on cow's milk. 14% were anemic at baseline.	6-8	100	SBRCT. Fair quality. 85/100 included in analysis due in part to exclusions after randomization.	Formula for 18 mos., then cow's milk until 24 mos.	Cash payment sufficient to buy 500 ml of cow's milk daily for 24 mos.	Griffith's.	18, 24	No difference at 18 months. At 24 months, + difference in global developmental quotient (+5.4 points).

Panel 2. Supplementation in developed countries (continued)										
Trial	Setting	Subjects	Age (mos.)	N	Design Characteristics	Treatment (duration)	Control	Follow-up Assessment	Time (mos.)	Results
Morley, 1999 ⁵⁹	Average-risk area, Leicester, Norwich, and Nottingham, England	Healthy full-term infants on pasteurized cow's milk.	9	493	SBRCT. Fair-quality. 428/493 included in analysis.	Formula containing 0.9 mg/liter iron or formula containing 1.2 mg/liter iron.	Continue on cows' milk (estimated to contain 0.05 mg iron/liter).	BSID.	18	No differences.
Friel, 2003 ⁶⁷	Average-risk area, Newfoundland, Canada	Healthy, breastfed infants	1	77	DBRCT. Fair-to-poor; small, underpowered study with a high dropout rate. 77, 56, 51, and 44 infants were seen at 1, 3.5, 6, and 12 mos.	Oral iron syrup from 1 to 6 mos. of age.	Placebo as syrup alone.	BSID.	13	PDI (100 ± 12 vs. 93 ± 9; normal range 85 to 115) MDI scores did not differ. Trend (P = .07) for improved visual acuity.
Metallinos-Katsaras, 2004 ⁶⁸	Low-income, high-risk area day-care centers in Athens, Greece.	Healthy children except for low iron intake.	3-4 years	49	RCT. Fair quality. Allocation concealment, blinding not discussed.	MV for 2 mos., then MV plus either 15mg iron in the form of ferrous fumarate or placebo for 2 mos.	Placebo.	Reaction time, a continuous performance task (CPT), and 3 oddity learning (OL) tasks.	2	In ITT analysis, for "suspected anemic" subjects only, treatment improved reaction time (P<0.05), speed of discrimination (P<0.05), and CPT efficiency (P<0.10).

BSID = Bayley Scales of Infant Development, DBRCT = Double-blinded randomized controlled trial, ITT = Intention to treat, MDI = Mental Development Index, MV = Multivitamin, PDI = Psychomotor Development Index, RCT = Randomized controlled trial, SBRCT = Single-blinded randomized controlled trial