Anemia, iron deficiency, and iron deficiency anemia in 12–36-mo-old children from low-income families1–3

Julie M Schneider, Mary L Fujii, Catherine L Lamp, Bo Lönnerdal, Kathryn G Dewey, and Sheri Zidenberg-Cherr

ABSTRACT
Background: Iron deficiency (ID) is the most common nutritional deficiency in the world and remains relatively common in at-risk groups in the United States. The actual prevalence of anemia, ID, and iron deficiency anemia (IDA) in California remains unclear.

Objective: The objective was to determine the prevalence of anemia, low iron stores, ID, and IDA in children participating in the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) population, and to assess the value of using hemoglobin to predict ID.

Design: This was a cross-sectional study of a convenience sample of 12–36-mo-old children from WIC clinics in 2 California counties.

Results: The prevalence of anemia was 11.1% (hemoglobin <110 g/L at 12–24 mo or <111 g/L at 24–36 mo). Study- and literature-determined abnormal values for iron measures were as follows: serum ferritin ≥8.7 or <10.0 μg/L, serum transferrin receptor ≥8.4 or >10.0 μg/mL, and transferrin saturation ≤13.2% or <10.0%, respectively. The prevalences of low iron stores (low ferritin) were 24.8% and 29.0%, of ID (≥2 abnormal iron measures) were 16.2% and 8.8%, and of IDA (ID with low hemoglobin) were 3.4% and 3.2% on the basis of study- and literature-determined cutoffs, respectively. Hemoglobin concentration was used to predict study- and literature-determined ID on the basis of receiver operating characteristic curves. The sensitivity of low hemoglobin in predicting study- and literature-determined ID was low (23.2% and 40.0%, respectively).

Conclusions: Anemia and ID were prevalent in this WIC sample, but IDA was uncommon. Low hemoglobin is a poor predictor of ID. Am J Clin Nutr 2005;82:1269–75.

KEY WORDS Iron deficiency, anemia, toddlers, serum ferritin, serum transferrin receptors, transferrin saturation, WIC, Special Supplemental Nutrition Program for Women, Infants and Children

INTRODUCTION
Iron deficiency is the most common nutrient deficiency in the world. Symptoms of iron deficiency are subtle and nonspecific and often only become apparent with severe anemia. Infants and children with iron deficiency, with or without anemia, have been characterized with impaired neurodevelopment (1–5), such as longer sensory pathway transmission (6, 7). Relative to healthy infants, infants with iron deficiency anemia are more wary, hesitant, and easily tired; are less active; are less attentive to instructions and demonstrations; and tend to stay closer to their caregivers. It has been suggested that these behaviors may contribute to impaired development through functional isolation (2, 8). The brain’s sensitivity to iron deficiency is mitigated by the severity and timing of the deprivation, and the adverse effects of iron deficiency may or may not be reversible (9–11).

Although the prevalence of iron deficiency anemia in the United States has decreased over the past decade, data from many surveys indicate that it remains relatively high among low-income, preschool-age children. The US Centers for Disease Control and Prevention reported a prevalence of 7% for iron deficiency and 2% for iron deficiency anemia in 1- to 2-y-old children from all income levels (12). In contrast, the prevalence of iron deficiency was 17% for 1–2 y olds and 6% for 3–4 y olds among Mexican American toddlers, and 12% for 1–2 y olds and 5% for 3–4 y olds in low income (≤130% of poverty threshold) households (13). One objective stated in Healthy People 2010 is to reduce iron deficiency in 1- to 2-y-old children to 5% (compared with the 1988–1994-baseline prevalence of 9%) and in 3- to 4-y-old children to 1% (compared with the 1988–1994-baseline prevalence of 4%) in all children by 2010 (13).

Several approaches are used to assess the iron status of an individual or of a population. Although the use of multiple tests (14, 15) is an appropriate approach to assess the iron status of a population, it is less practical and not commonly used in clinical settings. Iron deficiency anemia is more commonly defined with 1–2 indicators in clinical settings; most clinical cases report only anemia (based on hemoglobin or hematocrit values). As a result, the actual prevalence of iron deficiency and iron deficiency anemia among low-income 12–36-mo-olds is unclear.

In the current study, multiple measures of iron status, including serum ferritin, serum transferrin receptor, and transferrin saturation, were used to assess iron status. Hemoglobin was used to assess anemia. Iron deficiency and iron deficiency anemia were determined in a convenience sample of children aged 12-36 mo from low-income families who were attending selected Special Supplemental Nutrition Program for Women, Infants and

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Children (WIC) clinics. The information gathered was intended to produce estimates of iron deficiency and iron deficiency anemia and determine the predictive value of hemoglobin in identifying iron deficiency.

SUBJECTS AND METHODS

Study population

The, 12–36-mo-old participants were recruited from California WIC waiting rooms between August 2000 and June 2002. The WIC clinics are located in Contra Costa County (Richmond) and Tulare County (Earlimart and Dinuba). Richmond is an urban community with a population of ≈99 216, whereas Earlimart and Dinuba have populations of 5881 and 16 849, respectively (16). Hispanics and Latinos constitute ≈27%, 75%, and 88% of the populations in Richmond, Dinuba, and Earlimart, respectively (17). The median household incomes in Richmond, Dinuba, and Earlimart are ≈$44 000, $33 000, and $21 000, respectively, and 13%, 21%, and 38% of the families in these 3 counties fall below the poverty level (17). The Richmond clinic has ≈6800 WIC participants, Earlimart has ≈1600 WIC participants, and Dinuba has ≈3800 WIC participants.

Trained bilingual (English and Spanish), bicultural interviewers (1 per county) approached all women in the WIC waiting rooms to recruit subjects for the study, 3–4 d/wk. The interviewers were instructed to introduce themselves, briefly describe the study, and ask the women whether they had a child between 12 and 36 mo of age. Men were excluded because the interview included questions pertaining to pregnancy (data not shown). Subsequently, the interviewers asked whether the mothers would like to participate in the study. Approximately 673 women with children aged 12–36 mo were approached, and 498 gave consent to participate in the study (≈74% of those who were eligible). To be eligible for the study, a mother could not have received information about iron deficiency anemia from a doctor or nurse, because this may have influenced feeding behaviors (only one mother with a child in the target age range was excluded for this reason). Written informed consent was obtained from the mothers before participation in the study, and the University of California, Davis, Institutional Review Board approved the study protocol.

Laboratory analysis

Venous blood samples were collected from the toddlers by phlebotomists in laboratories adjoining the respective WIC sites from 0900 to 1900. The subjects were not required to fast. For serum collection, blood (≈3 mL) was collected into trace mineral–free tubes (Vacutainer; Becton Dickinson, Plymouth, United Kingdom) and allowed to coagulate (≈45 min) at room temperature. The coagulated blood was centrifuged at 1315 × g for 8 min at 25 °C. Serum was divided into aliquots for the measurement of ferritin, transferrin receptors, transferrin saturation, and C-reactive protein (CRP). Whole blood (≈3 mL) was collected into EDTA-containing tubes (Vacutainer) for automated blood analysis. Capillary samples were obtained on the same day as were the venous samples from a subgroup of children and were analyzed with a Hemocue B-Hemoglobin system (Angelholm, Sweden).

Serum samples were transported on dry ice to the University of California, Davis, and stored at −80 °C. Batches of 50–100 samples were analyzed for serum ferritin with an immunoradiometric assay (Coat-A-Count Ferritin; Diagnostic Products, Inc, Los Angeles, CA), serum transferrin receptor with a human transferrin receptor immunoassay kit (Ramco, Houston, TX), serum transferrin with a nephelometric assay (Beckman Coulter, Brea, CA), serum iron (18) with atomic absorption spectrophotometry (model 300; Perkin-Elmer, Boston, MA), and serum CRP by radial immunodiffusion (Nanorid; The Binding Site, Birmingham, United Kingdom). Transferrin saturation was determined on the basis of serum transferrin and serum iron concentrations. Total iron binding capacity (TIBC) was calculated as serum transferrin/0.68 (19). The percentage of transferrin saturation was subsequently calculated as (serum iron/TIBC) × 100 (20).

Hemoglobin was determined with the use of automated analyzers at the Tom Powers Richmond Health Center Clinical Laboratory for the Richmond clinic (Coulter Max M; Coulter, Fullerton, CA) and was transported to Unilab for the Earlimart clinic (Abbott Cell-Dyn 4000; Abbott Park, IL) or to the Hillman Health Center Clinical Laboratory in Tulare, CA, for the Dinuba clinic (Abbott Cell-Dyn 3200).

Statistical analysis

General statistical analyses

Frequencies were run for prevalence data. Chi-square or Fisher’s exact test was used to compare proportions, and t tests were used to compare means. Odds ratios and 95% CIs were calculated by using logistic regression analysis for anemia, low iron stores, and iron deficiency anemia. Receiver operator characteristic (ROC) curves, area under the curve (AUC), sensitivity, and specificity were used to determine the performance of hemoglobin concentration in the diagnosis of iron deficiency. All analyses using iron-status variables other than hemoglobin excluded children whose serum showed evidence of hemolysis or who had an elevated CRP concentration (≥10 mg/L) (21). The sample size calculation was based on an estimate of the prevalence of anemia, assuming an approximate prevalence of 15% and an error of 3.5% (probability = 0.15, α = 0.05). This calculation indicated a need to recruit 400 children; however, 500 children were recruited to allow for unsuccessful blood draws, hemolyzed samples, and elevated CRP concentrations. Both ferritin and transferrin receptors had skewed distributions; therefore, these values were log transformed for all statistical calculations and converted back to the original units as geometric means and SDs. Statistically significant results were those with values of P ≤ 0.05. All statistical analyses were performed by using SPSS software (version 10.0; SPSS, Inc, Chicago).

Determination of abnormal values for low iron stores, iron deficiency, and iron deficiency anemia

A multiple-indicator model was used to define iron deficiency on the basis of ≥2 of 3 abnormal values for ferritin, transferrin receptors, or transferrin saturation. Iron deficiency anemia was defined as having iron deficiency and low hemoglobin. Low hemoglobin was defined as hemoglobin <110 g/L for 12–24-mo-olds or <111 g/L for 24–36-mo-olds (22).

To determine abnormal values for ferritin, transferrin receptors, and transferrin saturation, hemoglobin (dependent variable) was regressed on each iron-status variable (independent variable) by using a 2-phase segmented linear regression model (SAS

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for WINDOWS release 8; SAS Institute Inc, Cary, NC). Segmented regression analysis determined that the breakpoints were as follows: low ferritin, ≤8.7 μg/L (95% CI: 6.8, 11.1 μg/L); high transferrin receptor, ≥8.4 μg/mL (95% CI: 7.2, 9.7 μg/mL); and low transferrin saturation, ≤13.2% (95% CI: 8.9%, 17.6%). Segmented linear regression allows for data to be described by ≥2 regression equations for the independent variable, preceding and following ≥1 flex point. The join model, a continuous value for each regression, was used to determine the abnormal values. Cases below the lowest detectible limit for ferritin (<5.0 μg/L) were excluded from the determination of the flex point for low ferritin values. The flex points were determined in children whose serum showed no evidence of hemolysis and did not have an elevated CRP concentration (≥10 mg/dL) (21). The prevalences of low iron stores (low serum ferritin), iron deficiency, and iron deficiency anemia were compared with those from previous studies by using both the study-determined and literature-determined cutoffs. For the literature-determined cutoffs, low iron stores were defined as serum ferritin <10 μg/L (12, 23). Iron deficiency based on literature-determined cutoffs was defined as ≥2 of 3 abnormal values for ferritin, transferrin receptors (>10 μg/mL), and transferrin saturation (>10%) (12, 24, 25).

Regression against hemoglobin is informative in identifying cutoff values (flex point) for the iron measures, because hemoglobin declines when abnormal values are reached. Hemoglobin is a late indicator of iron deficiency, and it can be argued that a cutoff below this biological threshold would be more useful. Results of the analyses showed that the study-determined cutoffs were less restrictive for transferrin receptors and transferrin saturation than were the cutoffs used by Olivares et al (24) and Looker et al (23).

**RESULTS**

A summary of the subjects included in the analysis is shown in Figure 1. Thirty-three children had elevated serum CRP, 32 children had evidence of hemolysis, and 3 had both. In total, 425 subjects provided data on anemia and 355 provided data on iron status. Subjects with normal serum CRP and no evidence of hemolysis who had only 2 of the 3 iron measures were retained for analysis if they could be clearly delineated as iron deficient or iron sufficient on the basis of both study- and literature-determined iron deficiency cutoffs; only 3 such subjects could not be classified and were excluded from the analysis.

The ethnic breakdown of the sample was as follows: 403 (93.3%) Latinos, Hispanics, or Mexican Americans; 15 (3.5%) African Americans; 5 (1.2%) non-Hispanic whites; 3 (0.7%) multiethnic; 2 (0.5%) Asians or Pacific Islanders; 2 (0.5%) Native Americans, and 2 (0.5%) unknown. The average age was 23.2 ± 6.7 mo (range: 12.0–35.8 mo). The sample was composed of 52.3% boys and 47.7% girls.

The prevalence of anemia was 11.1% (47 of the 425 children with hemoglobin values). The prevalences of anemia, low iron stores, iron deficiency, and iron deficiency anemia on the basis of study-determined and literature-determined cutoffs are presented in Table 1 for boys and girls. The boys had a significantly greater prevalence of both study- and literature-determined low iron stores and iron deficiency than did the girls. Prevalence estimates did not differ significantly between 12–24-mo-olds and 24–36-mo-olds for anemia, low iron stores, iron deficiency, or iron deficiency anemia. The exclusion of children with elevated serum CRP concentrations may have biased the prevalence estimates for iron deficiency. Although mean transferrin saturation was significantly lower in children with elevated CRP concentrations than in those with normal CRP concentrations, there was no significant difference in mean transferrin receptor concentrations (data not shown). The inclusion of children with elevated CRP concentrations did not change the prevalence estimates for iron deficiency (data not shown).

The mean (±SD) hemoglobin concentration for the 34 subjects with both capillary and venous samples was 122.3 ± 10.6 and 119.0 ± 8.2 g/L, respectively (P = 0.026, paired t test). The odds ratios for anemia, low iron stores, and iron deficiency were not significantly greater for low-birth-weight (<2500 g) children than for normal-birth-weight children (≥2500 g) (Table 2), but there were only 27 children with birth weights <2500 g. There was no significant difference in sex or age between low-birth-weight children and normal-birth-weight children.

The odds ratios for anemia in iron-deficient children relative to iron-sufficient children are shown in Table 3 by study-determined and literature-determined values, respectively. The odds of anemia was greater in children who had iron deficiency, low ferritin, high transferrin receptors, and low transferrin saturation than in children who were iron sufficient or had adequate values for ferritin, transferrin receptors, and transferrin saturation. Hemoglobin concentration was used to predict iron deficiency on the basis of ROC curves (Table 4). The sensitivity at the anemia cutoff was ≈23% for study-determined iron deficiency and 40% for literature-determined iron deficiency.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Flow diagram of subjects included in the cross-sectional analysis of anemia, low iron stores, and iron deficiency. Hb, hemoglobin; CRP, C-reactive protein. “Iron measures” includes serum ferritin, serum transferrin receptors, and serum transferrin saturation.
Anemia
Iron deficiency
Study-determined cutoffs
Low iron stores
Iron deficiency
Iron deficiency anemia
Literature-determined cutoffs
Low iron stores
Iron deficiency
Iron deficiency anemia

40% for study- and literature-determined cutoffs, respectively). Had a low sensitivity for predicting iron deficiency (23% and
low hemoglobin concentrations and iron deficiency, hemoglobin
deficiency. Although there was a significant relation between
effect of age.

A low hemoglobin value is an
sole use of hemoglobin values to screen children will not identify
the number of children falsely categorized as iron sufficient when, in
fact, they were actually iron deficient with or without anemia (ie,
reduced sensitivity).

The prevalence of anemia was 11% for this sample compared with the Pediatric Nutrition Surveillance System
(PedNSS) report of 14–15% in California for 12–35-mo-olds in
2002 (28) and 13.1% nationally for children aged <5 y in 2001
(29). PedNSS defines anemia as either low hemoglobin or low
hematocrit values. Our study and PedNSS used the same cutoffs
for hemoglobin (22); however, PedNSS reports anemia data from
capillary, venipuncture, or both capillary and venipuncture
samples. These are critical considerations for comparisons of the
prevalence of anemia across studies, because hemoglobin values
can vary based on the method used. Thus, it is conceivable that
the prevalence data obtained in our study differ from those
reported in the PedNSS as a result of the multiple methods used to
obtain blood throughout the state in clinics that report to PedNSS.
Another possibility is that our prevalence estimate is biased by the
inability to collect samples from the children whose mothers
decided to participate (≈26% of those who were eligible). If
these children were at higher risk of anemia than those whose
mothers agreed to participate, the prevalence of 11% would be an
underestimate.

Confirmation of iron deficiency anemia should be made on the
basis of iron measures in addition to hemoglobin. Values
commonly considered low for serum ferritin are 10–12 μg/L (12, 20,
30). We selected 10 μg/L as a cutoff for serum ferritin to be
consistent with the most recent National Health and Nutrition
Examination Survey (NHANES) on the prevalence of iron defi-
ciency in the United States (12). The cutoff for transferrin satu-
ratation was also selected from the NHANES report (12). There are
only a relatively small number of studies on transferrin receptors
in children aged 12–36 mo. However, a 2-site study in Honduras
and Sweden determined a cutoff of 11 μg/mL for transferrin

There were no significant sex-by-age interactions and no significant
effect of age.

Defined as hemoglobin <110 g/L (12–24 mo) or <111 g/L (24–36
mo) (20, 29).

Defined as ferritin ≤8.7 μg/L.

Significantly different from boys (chi-square test): \( P < 0.050,\)

Defined as ≥2 of 3 abnormal values for ferritin ≤8.7 μg/L, transferrin
receptors ≥8.4 μg/mL, or transferrin saturation ≤13.2%.

Defined as ≥2 of 3 abnormal values for ferritin ≤8.7 μg/L, transferrin
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transferrin receptors >10.0 μg/mL (23), or transferrin saturation <10.0% (12, 24).

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DISCUSSION

The results of this study are consistent with the concept that the
sole use of hemoglobin values to screen children will not identify
all those who are iron deficient. A low hemoglobin value is an
effective indicator of iron deficiency when the prevalence of iron
deficiency is high (21). However, iron deficiency in the United
States has decreased, which has made anemia screening for iron
deficiency less effective (12, 21, 26). We used ROC curves to
evaluate the predictive value of hemoglobin for identifying iron
deficiency. Although there was a significant relation between
low hemoglobin concentrations and iron deficiency, hemoglobin
had a low sensitivity for predicting iron deficiency (23% and
40% for study- and literature-determined cutoffs, respectively).
Thus, ≈77% and ≈60% of the iron-deficient children would not
have been identified on the basis of study- and literature-
determined cutoffs. Furthermore, our values were determined
from samples obtained through venipuncture by using automated
analyzers in clinical laboratories. At the WIC sites where our data
were collected, hemoglobin is typically determined by finger-
prick collection in nearby clinics. Had we used capillary samples,
it is possible that more children would have been misdiagnosed
as iron sufficient because hemoglobin values for capillary
samples tend to be elevated (27). The difference in the mean hemog-
lobin values for children with both capillary and venous samples
was ≈3.2 g/L. Had all the venous hemoglobin values increased by 3.2 g/L, the prevalence of anemia would have decreased from 11.1% to 6.4%. This would have increased the number of children falsely categorized as iron sufficient when, in
fact, they were actually iron deficient with or without anemia (ie,
reduced sensitivity).

The prevalence of anemia was ≈11% for this sample compared with the Pediatric Nutrition Surveillance System
(PedNSS) report of 14–15% in California for 12–35-mo-olds in
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in children aged 12–36 mo. However, a 2-site study in Honduras
and Sweden determined a cutoff of 11 μg/mL for transferrin

TABLE 1
Prevalence of anemia, low iron stores, and iron deficiency in low-income male and female children aged 12–36 mo

<table>
<thead>
<tr>
<th></th>
<th>Boys (%)</th>
<th>Girls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>9.9 (22 of 223)</td>
<td>12.4 (25 of 202)</td>
</tr>
<tr>
<td>Study-determined cutoffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low iron stores</td>
<td>29.1 (55 of 189)</td>
<td>19.9* (33 of 166)</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>19.8 (37 of 187)</td>
<td>12.1 (20 of 165)</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>3.2 (6 of 185)</td>
<td>3.7 (6 of 163)</td>
</tr>
<tr>
<td>Literature-determined cutoffs</td>
<td></td>
<td></td>
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<tr>
<td>Low iron stores</td>
<td>34.9 (66 of 189)</td>
<td>22.3* (37 of 166)</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>10.2 (19 of 187)</td>
<td>7.3 (12 of 165)</td>
</tr>
<tr>
<td>Iron deficiency anemia</td>
<td>2.7 (5 of 185)</td>
<td>3.7 (6 of 163)</td>
</tr>
</tbody>
</table>

*Defined as hemoglobin <110 g/L (12–24 mo) or <111 g/L (24–36 mo) (20, 29).

*Defined as ferritin ≤8.7 μg/L.

Significantly different from boys (chi-square test): \( P < 0.050,\)

Defined as ≥2 of 3 abnormal values for ferritin ≤8.7 μg/L, transferrin
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**TABLE 2**
Odds ratios (ORs) and 95% CIs for anemia, low iron stores, and iron deficiency for low-birth-weight (LBW; <2500 g) and normal-birth-weight (NBW; ≥2500 g) children

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>LBW children</th>
<th>NBW children</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>with abnormal values</td>
<td>with abnormal values</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.67 (0.15, 2.91)</td>
<td>2 of 26</td>
<td>44 of 395</td>
</tr>
<tr>
<td>Low iron stores</td>
<td>1.56 (0.57, 4.29)</td>
<td>6 of 18</td>
<td>79 of 334</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>2.81 (1.00, 7.83)</td>
<td>6 of 18</td>
<td>50 of 331</td>
</tr>
</tbody>
</table>

*Defined as hemoglobin <110 g/L (12–24 mo) or hemoglobin <111 g/L (24–36 mo) (20, 29).

*Defined as ferritin ≤8.7 μg/L.

*Defined as ≥2 of 3 abnormal values for ferritin ≤8.7 μg/L, transferrin receptors ≥8.4 μg/mL, or transferrin saturation ≤13.2%.
receptors in 4- to 9-mo-old children (31). In a study in Chile, infants between 9 and 15 mo had a mean (±SD) transferrin receptor concentration of 12.0 ± 4.6 μg/mL when hemoglobin was 100–109 g/L and a mean transferrin receptor concentration of 16.1 ± 7.7 μg/mL when hemoglobin was <100 g/L. The investigators found that when transferrin receptors were >10 μg/mL, there was a sensitivity of 66% and a specificity of 71% for iron deficiency (24). Because the children in our study were older, a lower abnormal value for transferrin receptor concentration was expected (32–34), and the literature cutoff for transferrin receptor concentration was selected at <10 μg/mL.

Approximately 30–35% of the boys and 20–22% of the girls had low iron stores (low serum ferritin) on the basis of the study- and literature-determined cutoffs, respectively. The prevalence of low iron stores is substantially higher than the 18% prevalence of low iron status reported for 1–3-y-old children attending well-child visits at 4 pediatric offices in New York (35). This finding is not surprising because the current study recruited subjects from WIC, which preferentially enrolls children who are at high risk of iron deficiency. The New York study comprised children from lower- and middle-socioeconomic groups and from a population that was only ≈40% Hispanic.

We did not find an increased risk of anemia, low iron stores, or iron deficiency in low-weight children, although the odds ratio of ≈3 for iron deficiency is notable (Table 2). Compared with normal-weight infants, low-weight-infants have smaller iron stores, which are taxed by subsequent catch-up growth and red blood cell gains (25, 36). We expected that low-birth-weight children would be more likely to be anemic, have low iron stores, or be iron deficient. However, only 27 of the 432 subjects were low-birth-weight infants; thus, the power to detect a significantly increased risk was low.

As evident in Table 3, the children who had iron deficiency or abnormal iron status values were more likely to be anemic, regardless of whether study- or literature-determined cutoffs were used. Iron-deficient children had a risk of anemia that was 3 times and 7 times that of iron-sufficient children on the basis of the study- and literature-determined cutoffs. These differences in the risk of anemia among study- and literature-determined iron deficiencies were largely due to the more stringent cutoff of 10 μg/mL, rather than 8.4 μg/mL, for transferrin receptors. Compared with children with adequate ferritin concentrations, children with low ferritin concentrations were also more likely to be anemic on the basis of both the study- and literature-determined cutoffs. Children with transferrin receptor concentrations >10 μg/mL had a risk of anemia 6 times that of children with transferrin receptor concentrations ≤10 μg/mL; however, when the cutoff for transferrin receptor concentrations was ≥8.4 μg/mL, children with elevated concentrations did not have a greater risk of anemia. This indicates that transferrin receptors may be a good biomarker for iron deficiency. A transferrin receptor concentration >10 μg/mL indicates anemia; however, at the study-determined cutoff of ≥8.4 μg/mL, the

<table>
<thead>
<tr>
<th>Cutoff</th>
<th>OR (95% CI)</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>n</th>
<th>OR (95% CI)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study-determined</td>
<td>3.404 (1.66, 6.96)</td>
<td>348</td>
<td>1.78 (0.83, 3.83)</td>
<td>348</td>
<td>1.84 (0.84, 4.05)</td>
<td>343</td>
<td>3.194 (1.48, 6.87)</td>
<td>348</td>
</tr>
<tr>
<td>Literature-determined</td>
<td>2.620 (1.29, 5.32)</td>
<td>348</td>
<td>6.190 (2.60, 14.74)</td>
<td>348</td>
<td>3.340 (1.38, 8.16)</td>
<td>343</td>
<td>7.090 (3.03, 16.61)</td>
<td>348</td>
</tr>
</tbody>
</table>

1. Anemia was defined as hemoglobin <110 g/L (12–24 mo) or hemoglobin <111 g/L (24–36 mo) (20, 29).
2. Study-determined and literature-determined low ferritin defined as ≤8.7 and <10 μg/L (12, 21), respectively.
3. Study-determined and literature-determined high transferrin receptor defined as ≥8.4 and >10 μg/mL (23), respectively.
4. Study-determined and literature-determined low transferrin saturation defined as ≤13.2% and <10% (12, 24), respectively.
5. Study-determined cutoffs for iron deficiency: ≥2 of 3 abnormal values for ferritin ≤8.7 μg/L, transferrin receptors ≥8.4 μg/mL, or transferrin saturation ≤13.2%.
6. Literature-determined cutoffs for iron deficiency: ≥2 of 3 abnormal values for ferritin <10.0 μg/L (12, 21), transferrin receptors >10.0 μg/mL (23), or transferrin saturation <10.0% (12, 24).
7–9. Significant in those with abnormal laboratory values (chi-square test): 7 P ≤ 0.001, 8 P ≤ 0.005, 9 P ≤ 0.05.

TABLE 4
Receiver operator characteristic curves of hemoglobin in predicting iron deficiency and corresponding sensitivity and specificity at anemic levels

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>AUC</th>
<th>P</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Percentage misclassification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study-determined iron deficiency</td>
<td>0.692</td>
<td>&lt;0.001</td>
<td>0.232</td>
<td>0.904</td>
<td>20.4</td>
</tr>
<tr>
<td>Literature-determined iron deficiency</td>
<td>0.767</td>
<td>&lt;0.001</td>
<td>0.400</td>
<td>0.909</td>
<td>13.5</td>
</tr>
</tbody>
</table>

1. n = 348. Anemia was defined as hemoglobin <110 g/L (12–24 mo) or hemoglobin <111 g/L (24–36 mo) (20, 29). AUC, area under the curve.
3. Study-determined cutoff for iron deficiency: ≥2 of 3 abnormal values for ferritin ≤8.7 μg/L, transferrin receptors ≥8.4 μg/mL, or transferrin saturation ≤13.2%.
4. Literature-determined cutoff for iron deficiency: ≥2 of 3 abnormal values for ferritin <10.0 μg/L (12, 21), transferrin receptors >10.0 μg/mL (23), or transferrin saturation <10.0% (12, 24).

TABLE 3
Odds ratios (ORs) and 95% CIs for anemia in children with study-determined abnormal values for iron deficiency, low ferritin, high transferrin receptors, and low transferrin saturation
transferrin receptor concentration may better reflect poor iron status before the onset of anemia.

Although there has been a steady decline in the prevalence of anemia in the United States (37), iron deficiency remains high in several subgroups. In a 5-state study, Sherry et al (38) reported a decline in the prevalence of anemia on the basis of hematocrit only. The decline was attributed to better iron nutrition, but the authors acknowledged that the 5-state study did not measure additional iron indexes. In contrast, using multiple indicators of iron deficiency, we observed a 16% prevalence of iron deficiency, which is a substantially higher value than is the Healthy People 2010 goal of 1–5% (13).

The challenges of reducing anemia and iron deficiency in high-risk populations, such as toddlers, have been addressed through programs such as WIC, the iron fortification of infant formulas and cereals, and surveillance monitoring by PedNSS and NHANES. WIC enrolls women and children who are at the highest risk of anemia and iron deficiency and provides vouchers to purchase WIC-approved foods, including, but not limited to, iron-fortified cereals, iron-rich formulas and infant cereals, juice, and beans. The WIC program screens children for low hemoglobin to educate and reduce the incidence of anemia in their population. There is a need to identify children with depleted iron stores and iron deficiency before they develop iron deficiency anemia. We question the validity of focusing efforts only on reducing anemia and ignoring the need to detect and treat iron deficiency. This is especially significant given recent findings that iron deficiency without anemia has been associated with developmental delays (5). In addition, Konofal et al (39) reported that low ferritin concentrations were correlated with more severe attention deficit hyperactivity disorder symptoms and suggest that low iron stores contribute to attention deficit hyperactivity disorders in children. Given the severity of the consequences of iron deficiency anemia, including delayed psychomotor development and impaired cognitive performance (2, 30), impaired growth, and increased morbidity, it is evident that additional efforts are needed to reduce iron deficiency in at-risk populations. In addition to identifying children with iron deficiency, we recommend that health care providers educate all parents about iron-fortified cereals, iron-rich formulas and infant cereals, juice, and beans. The WIC program screens children for low hemoglobin to educate and reduce the incidence of anemia in their population. There is a need to identify children with depleted iron stores and iron deficiency before they develop iron deficiency anemia. We question the validity of focusing efforts only on reducing anemia and ignoring the need to detect and treat iron deficiency. This is especially significant given recent findings that iron deficiency without anemia has been associated with developmental delays (5). In addition, Konofal et al (39) reported that low ferritin concentrations were correlated with more severe attention deficit hyperactivity disorder symptoms and suggest that low iron stores contribute to attention deficit hyperactivity disorders in children. Given the severity of the consequences of iron deficiency anemia, including delayed psychomotor development and impaired cognitive performance (2, 30), impaired growth, and increased morbidity, it is evident that additional efforts are needed to reduce iron deficiency in at-risk populations.

REFERENCES


