Iron Deficiency and Cognitive Achievement Among School-Aged Children and Adolescents in the United States

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ABSTRACT. ***Context.*** **Iron deficiency anemia in infants can cause developmental problems. However, the relationship between iron status and cognitive achievement in older children is less clear.**

Objective. **To investigate the relationship between iron deficiency and cognitive test scores among a nationally representative sample of school-aged children and adolescents.**

Design. **The National Health and Nutrition Examination Survey III 1988–1994 provides cross-sectional data for children 6 to 16 years old and contains measures of iron status including transferrin saturation, free erythrocyte protoporphyrin, and serum ferritin. Children were considered iron-deficient if any 2 of these values were abnormal for age and gender, and standard hemoglobin values were used to detect anemia. Scores from standardized tests were compared for children with normal iron status, iron deficiency without anemia, and iron deficiency with anemia. Logistic regression was used to estimate the association of iron status and below average test scores, controlling for confounding factors.**

Results. **Among the 5398 children in the sample, 3% were iron-deficient. The prevalence of iron deficiency was highest among adolescent girls (8.7%). Average math scores were lower for children with iron deficiency with and without anemia, compared with children with normal iron status (86.4 and 87.4 vs 93.7). By logistic regression, children with iron deficiency had greater than twice the risk of scoring below average in math than did children with normal iron status (odds ratio: 2.3; 95% confidence interval: 1.1–4.4). This elevated risk was present even for iron-deficient children without anemia (odds ratio: 2.4; 95% confidence interval: 1.1–5.2).**

Conclusions. **We demonstrated lower standardized math scores among iron-deficient school-aged children and adolescents, including those with iron deficiency without anemia. Screening for iron deficiency without anemia may be warranted for children at risk.** ***Pediatrics*** **2001;107:1381–1386;** ***iron deficiency, anemia, cognition, math, children, adolescence.***

ABBREVIATION. NHANES, National Health and Nutrition Examination Survey.

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Iron deficiency is the most prevalent hematologic disorder in childhood.[1] Infants from 9 to 24 months of age may develop dietary iron deficiency as bone marrow stores of iron are depleted during a period of accelerated growth. Adolescent girls also are susceptible to dietary iron deficiency because of poor dietary intake in conjunction with high iron requirements related to rapid growth and menstrual blood loss. In a recent review of the prevalence of iron deficiency in the United States, 9% of toddlers and up to 11% of adolescent girls were iron-deficient.[2]

Iron deficiency is a systemic condition with many consequences including anemia, impaired exercise capacity, and functional alterations of the small bowel.[3] One of the most concerning consequences of iron deficiency in children is the alteration of behavior and cognitive performance. The association of iron deficiency anemia with lower mental and motor developmental test scores in early childhood is well-described and has recently been reviewed.[4–6] There are fewer published data, however, on cognitive achievement in iron-deficient school-aged children and adolescents; thus, the relationship between iron status and cognitive functioning for older children is less clear.[7–12]

The majority of studies evaluating cognitive performance and iron deficiency have focused on individuals who have iron deficiency anemia. There is little evidence to implicate iron deficiency without anemia in causing developmental problems.[4] However, central nervous system iron decreases before restriction of red cell production, and, therefore, the cognitive effects of iron deficiency may precede the hematologic manifestations of anemia.[13] Furthermore, the prevalence of iron deficiency without anemia is much greater than the prevalence of iron deficiency with anemia,[2] suggesting the potential for a greater public health impact. Although current screening guidelines recommend evaluation for anemia among certain children, there are no screening guidelines for evaluation for iron deficiency without anemia.[14]

The impact of iron deficiency on the cognitive functioning of older children, and, particularly, adolescent girls who are at highest risk for iron deficiency, requires clarification. The objective of this study was to evaluate the relationship between iron deficiency and standardized test scores among a nationally representative sample of 6- to 16-year-old US children. We considered this relationship both for children who had iron deficiency with anemia and for children who had iron deficiency without anemia.

METHODS

Population and Sampling

The National Health and Nutrition Examination Survey (NHANES) III is a large-scale national survey conducted by the National Center for Health Statistics.[15] Conducted from 1988 through 1994, in 2 phases of equal length and sample size, the survey includes a sample of ~40 000 persons. Both phase I and phase II include representative samples of the noninstitutionalized US population, 2 months of age and older, who live in households. The persons selected were asked to complete an extensive interview and an examination in a mobile examination center. The response rate for the interview component of the survey was 86%.

The NHANES III Household Youth Questionnaire was completed for 13 944 children and youths during the 6 years of NHANES III. Because only children between the ages of 6 years and 16 years performed the cognitive testing sections of the survey, we limited our analysis to these children ($n = 5398$). Hematologic profiles were completed for all examinees.

Independent Variables

Independent variables included standard demographic variables and poverty status (at or above or below the poverty level based on reported family income and the US Poverty Threshold produced annually by the US Census Bureau). Race was defined as white, black, Mexican American, or other races. Caretaker education (self-reported highest grade completed, categorized as less than high school education, high school education, or greater than high school education), and blood lead level (as a continuous variable) were also included. Laboratory values were measured using standard measurement assays, the details of which are described.[16,17]

Definitions of Iron Deficiency and Anemia

We used the definitions of iron deficiency and anemia previously used and described by Looker et al[2] in their evaluation of the prevalence of anemia in the United States using the same NHANES III database. The definition of iron deficiency was based on the 3 laboratory tests of iron status, including transferrin saturation, free erythrocyte protoporphyrin, and serum ferritin. An individual was considered iron-deficient if any 2 of these 3 values were abnormal for age and gender. Similarly, hemoglobin cutoffs were calculated based on the fifth percentiles for the reference groups (Table 1). Individuals were defined as having iron deficiency without anemia if they met the criteria for iron deficiency and had a hemoglobin value above the cutoffs referenced. We specifically considered this group of children because they would not be detected by a routine screen for hemoglobin as a marker of iron deficiency.

Cognitive Measures

The cognitive tests included in the NHANES III database consisted of portions of 2 standardized tests, the Wechsler Intelligence Scale for Children-Revised and the Wide Range Achievement Test-Revised. The Wechsler Intelligence Scale for Children-Revised contained 2 subtests, a verbal component (digit span) and a performance examination (block design). The Wide Range Achievement Test-Revised test contained math and reading components. All 4 of the tests that were available in NHANES were considered in this analysis. The tests were administered in the same order for all individuals, and scores were derived relative to the individual's age group based on test-specific standardized samples.

Analysis

Average test scores were compared (using Student's *t* test statistics for means and χ^2 tests for proportions) for children with normal iron status, iron deficiency without anemia, and iron deficiency with anemia. Cutoff values for test scores were determined by using the mean values for each individual test and creating a dichotomous variable for scores above or below the mean. Logistic regression was used for multivariate analysis predicting below average scores. Because NHANES III was based on a complex sampling design, appropriate sample weights were used in the analysis to produce national estimates. SUDAAN software was used to estimate associated variances and to obtain weighted frequencies, means, and standard errors.[18]

RESULTS

Among the 5398 children between the ages of 6 and 16 years included in the sample, 3% had iron deficiency. Using the criteria in Table 1 to define iron deficiency and anemia, the prevalence of iron deficiency without and with anemia also was determined for children with different age, gender, and demographic characteristics (Table 2). For each group that was considered, iron deficiency without anemia was more prevalent than was iron deficiency with anemia. Iron deficiency was relatively uncommon among 6- to 11-year-old children, with a prevalence <3%. In contrast, among 12- to 16-year-olds, iron deficiency was relatively common among the females, with a total prevalence of 8.7%. Most strikingly, although 7.2% of 12- to 16-year-old females manifested iron deficiency without anemia, only 1.5% had iron deficiency with anemia. Also, the prevalence of iron deficiency was >5% among Mexican American children, children of other racial backgrounds, and children living below the poverty level.

Table 3 shows average standardized scores for the math, reading, block design, and digit span tests by iron status. Results are shown for children with normal iron status, for iron-deficient children without anemia, and for iron-deficient children with anemia. Average math scores were lower for the iron-deficient children without anemia compared with children with normal iron status (87.4 vs 93.7; $P < .05$). The iron-deficient children with anemia also had math scores lower than did children with normal iron status (86.4 vs 93.7; $P < .05$). The only other test

TABLE 1. Cutoff Values for Iron Deficiency and Anemia

Age (Years)	Transferrin Saturation (%)	Serum Ferritin (ug/L)	Erythrocyte Protoporphyrin (μmol/L RBCs)	Mean Hemoglobin (g/L)
6–11	<14	<12	>1.24	<118
Female				
12–15	<14	<12	>1.24	<115
16	<15	<12	>1.24	<120
Male				
12–15	<14	<12	>1.24	<126
16	<15	<12	>1.24	<135

TABLE 2. Prevalence of Iron Deficiency by Demographic Patient Characteristics

Demographic Characteristic	*n*	Iron-Deficient Without Anemia (%)	Iron-Deficient With Anemia (%)	Iron-Deficient Total (%)
Age 6–11 y				
Females	1617	2.0	0.1	2.1
Males	1692	1.3	0.2	1.5
Age 12–16 y				
Females	1114	7.2	1.5	8.7
Males	975	0.8	0.1	0.9
Race				
White	1402	2.0	0.3	2.3
Black	1875	1.8	1.3	3.1
Mexican American	1874	5.3	0.8	6.1
Other	247	5.8	0.1	5.9
Poverty status				
Below poverty	1967	4.7	0.7	5.4
Above poverty	2991	1.8	0.4	2.2
Caretaker education				
$<$12th grade	2227	3.4	0.4	3.8
12th grade	1715	2.6	0.7	3.3
$>$12th grade	1417	2.2	0.3	2.5

TABLE 3. Average Standardized Test Scores for Children With and Without Iron Deficiency

	Normal Iron Status	Iron-Deficient Without Anemia	Iron-Deficient With Anemia
Math	93.7 ± 17.1	87.4 ± 15.6*	86.4 ± 15.9*
Reading	92.0 ± 17.5	90.5 ± 16.7	85.6 ± 16.4
Block design	9.5 ± 3.3	9.1 ± 3.3	8.0 ± 4.0*
Digit span	8.7 ± 2.9	8.6 ± 2.9	7.7 ± 3.7

$P < .05$ compared with children with normal iron status, using the Student's t test statistic.

that was significantly different among these groups of children was the block design test in iron-deficient children with anemia compared with children with normal iron status (8.0 vs 9.5; $P < .05$), but a similar trend of lower scores with diminishing iron status was seen for all of the other standardized tests that were measured.

Scores were subsequently dichotomized into an above or below average score to consider the percentage of children scoring below average for each category of iron status. As shown in Table 4, the percentage of children scoring below average in math was significantly higher ($P < .05$) for the iron-deficient children without anemia (71%) compared with children with normal iron status (49%). Although not statistically significant (likely related to the small numbers of children in the group), the percentage of iron-deficient children with anemia scoring below average in math also seemed higher compared with the children with normal iron status (72% vs 49%). The percentage of children scoring below average in reading, block design, and digit span did not differ by iron status.

TABLE 4. Percentage of Children Scoring Below Average by Iron Status

	Normal Iron Status (%)	Iron-Deficient Without Anemia (%)	Iron-Deficient With Anemia (%)
Math	49	71*	72
Reading	46	47	51
Block design	48	50	50
Digit span	46	47	48

$P < .01$ for difference compared with children with normal iron status by χ^2 analysis.

To evaluate the effect of iron status independent of potential confounding variables, a logistic regression analysis was performed predicting below average scores (Table 5). The analysis included an adjustment for age, gender, race, poverty status, caretaker education, and lead status. Results are shown for all iron-deficient children and for the subgroup of iron-deficient children without anemia. The iron-deficient children with anemia are included in the first group. They were not considered separately because of the small numbers of children with iron deficiency and anemia.

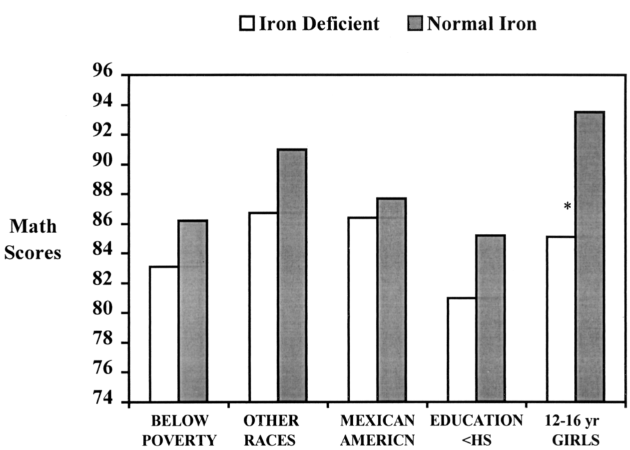
Even in this adjusted analysis, children with iron deficiency had a significantly elevated risk for scoring below average in math. Specifically, the odds ratio for scoring below average in math was 2.3 (95% confidence interval: 1.1–4.4) for all iron-deficient children, and 2.4 (95% confidence interval: 1.1–5.2) for the subgroup of iron-deficient children without anemia. Children with iron deficiency were not found to be at increased risk for scoring below average on reading, block design, and digit span tests.

To further characterize the impact of iron deficiency, math scores for children in subgroups with a high prevalence of iron deficiency were considered (Fig 1). In all subgroups of children considered (children living below the federal poverty level, children of other races, Mexican American children, children whose caretakers had less than a high school education, and 12- to 16-year-old girls), there was a trend for those with iron deficiency to have lower math scores compared with those with normal iron status. Among adolescent girls, these differences were statistically significant, with iron-deficient girls scoring an average of 85.1, compared with 93.5 for girls with normal iron status ($P = .003$).

TABLE 5. Logistic Regression Predicting Below Average Scores

	All Iron-Deficient Children			Iron-Deficient Without Anemia		
	Odds Ratio	95% Confidence Interval	*P* Value	Odds Ratio	95% Confidence Interval	*P* Value
Math	2.3*	(1.1,4.4)	.02	2.4*	(1.1,5.2)	.03
Reading	1.2	(0.6,2.2)	.5	1.2	(0.6,2.3)	.6
Block design	0.8	(0.4,1.3)	.3	0.8	(0.4,1.5)	.5
Digit span	0.9	(0.5,1.6)	.6	0.9	(0.4,1.8)	.7

Reference group = children with normal iron status.
* $P < .05$, adjusted for age, gender, race, poverty status, caretaker education, and lead status.



*P = .003 iron deficient compared to normal iron with t-test statistic

Fig 1. Math scores for children in subgroups with a high prevalence of iron deficiency.

DISCUSSION

Several biological mechanisms potentially link iron deficiency with impaired cognitive performance. Iron deficiency results in decreased body iron stores, including decreased iron in the central nervous system, even before red blood cell production is affected.[19] Disordered cerebral oxidative metabolism attributable to low levels of heme-containing and iron-dependent enzymes results in behavioral abnormalities in animals.[20] Furthermore, alterations of the metabolism of several putative neurotransmitters have been described in both iron-deficient animals and humans.[21]

Iron deficiency anemia is associated with developmental difficulties in infancy and early childhood.[22–27] Specifically, infants with iron deficiency anemia have lower scores on the Bayley Scale of Mental Development compared with iron-sufficient infants. Furthermore, behavioral and cognitive symptoms often improve with iron-replacement therapy, in many instances before an increase in the hemoglobin concentration.[21]

Only a few studies have considered the effect of iron deficiency on cognitive performance among older children and adolescents.[7–12] Initially, Webb and Oski[9] observed lower achievement test scores (including a math component) among school-aged children in Philadelphia who had a microcytic anemia. Although this study raised the possibility that iron deficiency affected academic performance, iron deficiency was not established as the cause of the microcytic anemia and potential confounding variables, such as poverty and race, were not considered.

After this observation, 3 trials in non-Western countries (Egypt, Indonesia, and Thailand) assessed the effect of iron supplementation on cognitive performance among school-aged children and adolescents.[10–12] Although the specific findings of these studies varied somewhat, each showed lower test scores among children with iron deficiency, compared with their iron-replete peers, thus providing reasonable evidence of an association between iron deficiency and some measures of cognition among children in these countries. One of these studies[10] found lower scores on achievement tests that included a math component. The impact of iron therapy in these studies was variable, with 2 studies suggesting a positive effect of therapy[10,11] and 1 study showing no effect.[12]

The most recent study performed in the United States was a randomized, controlled trial of iron supplementation in nonanemic iron-deficient adolescent girls.[8] The girls who received iron improved their scores in verbal learning and memory compared with controls. However, the sample size was small ($n = 78$), and no differences were found in the 3 tests of attention that were measured. Furthermore, the question of whether iron deficiency affected baseline measures of cognition was not addressed and math performance was not measured.

In this study, we evaluated data from a large, nationally representative sample of school-aged children and adolescents with and without iron deficiency and found lower standardized math scores among children with iron deficiency. Children with iron deficiency were more than twice as likely to score below average on math tests, even with adjustment for several potentially confounding variables. Furthermore, we demonstrated a relationship of poorer math scores among children who were iron-deficient without signs of anemia.

The impact of iron deficiency on cognition is best demonstrated among those children with the highest prevalence of iron deficiency. In all of the subgroups of children known to have a high prevalence of iron deficiency, there was a trend for the children with normal iron status to perform better on standardized math tests than children with iron deficiency. This difference in performance was most striking among the adolescent girls, who also have the highest prevalence of iron deficiency in this study. Past studies have shown a superiority of females in math achievement during elementary and middle school years and a reversal of this trend with male superiority (specifically in math problem solving), in high school and college years.[28] This study suggests that iron deficiency may contribute to this gender discrepancy by negatively affecting math performance among adolescent girls.

There are some potential limitations to this analysis. First, there are a limited number of cognitive measures available in the NHANES database; thus, the association of iron deficiency with other cognitive scores could not be assessed. Second, the small numbers of children in certain subgroups, particularly those with iron deficiency with anemia, may have limited the study's power to detect significant associations. In addition, many factors influence the cognitive functioning of children. Unmeasured variables, such as specific environmental disadvantages, could not be considered as potential confounding factors. It would be unlikely, however, for such variables to selectively alter the association of iron deficiency with math scores and not the other cognitive measures considered.

Because the NHANES survey is cross-sectional, a causal relationship between iron deficiency and cognitive scores could not be determined. Therefore, these data indicate only an association between iron deficiency and cognition. Finally, several studies have suggested that infants treated for iron deficiency anemia continue to have lower cognitive scores years later.[25,29–31] At least 1 study showed that iron-deficient young children had differential problems on the mathematics section of the Wide Range Achievement Test as long as 12 years after the episode of iron deficiency.[31] We cannot determine whether the iron-deficient children in this sample had iron deficiency as infants. Furthermore, it is not known whether the association of iron deficiency in older children and lower math scores would persist after treatment with iron.

The 3% of children with iron deficiency in this sample represent 1.2 million school-aged children and adolescents in the United States. Although the problem of iron deficiency among infants and toddlers has improved with iron supplementation of formulas and cereals, subgroups of older children remain at risk. The iron-deficient children without anemia represent the largest proportion of children with iron deficiency, suggesting the potential for the greatest public health implication. However, current guidelines that recommend only anemia screening would miss iron deficiency in this latter group of children.[14]

There is a need to confirm the observations from this study with a prospective study. If these data are confirmed, then screening for iron deficiency, particularly for those without anemia, might be warranted for high-risk children. It will be a challenge to identify the group of iron-deficient children without anemia. However, recently available laboratory tests, such as the reticulocyte hemoglobin content,[32] may provide a convenient and reliable means to detect iron deficiency without anemia in children and adolescents. Furthermore, a randomized trial will be needed to evaluate the effect of iron therapy on math performance. It is not yet clear whether identification of an at-risk group, general iron supplementation, or a combination of these efforts would provide the best approach to prevent the potentially negative cognitive effects of iron deficiency.

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THEORY-DRIVEN OBSERVATION

"How can anyone not see that all observation must be for or against some view if it is to be of any service?"

—Charles Darwin