Early childhood anemia and mild or moderate mental retardation[1–3]

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ABSTRACT

Background: Previous studies questioned the link between early childhood anemia and detrimental child development.

Objective: A population-based study was conducted to examine the association between early childhood anemia and mild or moderate metal retardation at 10 y of age.

Design: The present study linked early childhood nutrition data collected by the Special Supplemental Program for Women, Infants, and Children (WIC) and school records. Hemoglobin values were used to determine the relation between anemia in early life and children's placement in special education classes for mild or moderate mental retardation. Subjects were all participants in the WIC program. A computer program was used to link data from birth, WIC, and school records.

Results: Logistic regression showed an increased likelihood of mild or moderate mental retardation associated with anemia, independent of birth weight, maternal education, sex, race-ethnicity, the mother's age, or the child's age at entry into the WIC program.

Conclusion: These findings support the proposition that efforts to prevent mild and moderate mental retardation should include providing children with adequate nutrition during early childhood.   *Am J Clin Nutr* 1999;69:115–9.

KEY WORDS   Iron deficiency, anemia, mental retardation, child development, hemoglobin, children, data linkage, WIC program, Special Supplemental Program for Women, Infants, and Children

INTRODUCTION

In the past 20 y, possible long-term consequences of iron deficiency anemia on child development have become apparent. Recent studies have indicated that severe anemia affects both mental and motor development in children (1–8). It is unclear whether iron deficiency and its behavioral effects are correctable, particularly with regard to long-term developmental outcomes. Iron deficiency is most prevalent during the first 2 y of life when the infant brain is still developing. Severe iron deficiency anemia during this period may cause permanent neurologic damage (9). Biochemical studies of humans and animals have suggested an underlying neural mechanism linking iron deficiency and behavioral abnormalities, showing that iron deficiency is a biologically plausible cause of impaired development (10–13).

The effectiveness of intramuscular iron treatment in reversing both iron deficiency and the behavioral effects of this deficiency was first reported by Oski and Honig (14). Improvement in the mental development scores of nonanemic, iron-deficient infants after short-term, intramuscular treatment with iron was also reported (15). Some improvement in behavioral measures in toddlers or school-age children was found after treatment with oral supplements (3, 4). Most other studies investigating short-term effects found no improvement (1, 2).

More recent studies have reported that long-term effects of iron deficiency anemia during infancy may be permanent (5). Long-term or severe iron deficiency may not respond to iron therapy and may be associated with poorer outcomes at long-term follow-up even after iron therapy (2, 6, 7). Similar results have been reported when maternal education, social class, birth weight, and parental intelligence quotient were controlled (5–8). Some studies have suggested that severe or chronic iron deficiency may be associated with irreversible effects on brain development (2, 6, 7).

In response to the high rate of iron deficiency anemia and poor growth among low-income children, a federal effort to reduce the prevalence of iron deficiency, the Special Supplemental Program for Women, Infants, and Children (WIC), was started in 1973. Among the purposes of the WIC program is providing food supplements to low-income pregnant women, their infants, and children. Participation in the WIC program has resulted in improved nutritional status and increased birth weight among low-income children (16). However, the program's overall effectiveness is not yet clear (17).

The present study examined possible long-term effects of iron deficiency anemia on academic functioning in a sample of children at risk for inadequate nutrition. Information from birth records and WIC program records was related to the need for special education because of mild or moderate mental retardation.

SUBJECTS AND METHODS

Subjects

We linked the records of participants in the WIC program with birth and school records by using an automated computer linkage system. The birth record set consisted of all birth records in Dade County, FL, from 1979 and 1980. The school record set consisted of all school records from Dade County from 1990 and 1991. The WIC record set contained Dade County records for children who were born in 1979 or 1980 and participated in the WIC program between birth and 5 y of age. Birth records from Dade County for 1979 and 1980 were linked in a previous study with Dade County school records for 1990 and 1991 (18). This linkage, which will be referred to as the birth-school linkage, contained information on each subject at birth and at age 10 y (≈5th grade). This outcome age was selected because the rate of educational handicaps peaks in 10-y-olds (19). We linked the record sets by using the New York State Intelligence Information System code for last name, first name, date of birth, and sex. Codes and identifiers were chosen to be consistent with those used in a previous study (18). About 93% of eligible school records were linked with birth records.

The same method was used to link birth-school records with WIC Nutrition Surveillance records. Outcome analyses were then computed on this data set. These records will be referred to as the birth-school-nutrition linkage. Once all records were linked, identifiers were removed from the data. Thus, subject identity remained confidential. Records of 5411 subjects were found in all 3 data sources. About 69% of the sample was black, 23% was Hispanic, and 7% was white. The data linkage is described in **Figure 1**.

Variables

Anemia caused by severe iron deficiency is the third stage of iron deficiency, in which hemoglobin or hematocrit values are ≥2 SDs below age- and sex-specific references (9, 20). An inadequate amount of iron in the diet is the most common cause of anemia in US children, although there are other causes not related to nutrition. In large population groups in the United States, the hemoglobin concentration can serve as an effective index of iron nutrition status. In this study, low hemoglobin concentrations are used to represent the third stage of iron deficiency.

The variables included in the regression equation were hemoglobin, birth weight, maternal education, sex, race-ethnicity, age of mother, and age of child at entry into the WIC program. The prevalences and mean values of the study variables are shown in **Table 1**. Hemoglobin concentrations and age of child were reported by the WIC program and were retrieved from the WIC Nutrition Surveillance records. Hemoglobin concentrations were coded as grams per liter. Age of child at entry into the WIC program was coded in months. Birth weight, maternal education, sex, race-ethnicity, and age of mother were retrieved from the birth record. Birth weight was coded as very low (<1500 g), low (1500 to <2500 g), and normal (≥2500 g). Maternal education was coded as low (<12 y), normal (12 y), and high (>12 y). Race-ethnicity was coded as white, black, or Hispanic, and age of the mother was coded as <18, 18–35, and >35 y.

The outcome variable for the analyses was mild or moderate mental retardation on the basis of criteria used by the Florida Department of Education for special education placement. Mild or moderate mental retardation is defined as educable mentally handicapped or trainable mentally handicapped (21). This information was retrieved from the school record.

Procedure

We used logistic regression to estimate the association between anemia and mild or moderate mental retardation while controlling for birth weight, maternal education, sex, race-ethnicity, age of mother, and age of child. The main effect of each variable on the outcome was estimated while controlling for all other variables in the equation. Analyses were conducted with SPSS (SPSS Inc, Chicago).

The inverse of the hemoglobin concentration (to maintain positive directionality of the results) and the age of the child were entered into the regression equation as continuous variables. Hemoglobin measures were collected for subjects at the time of
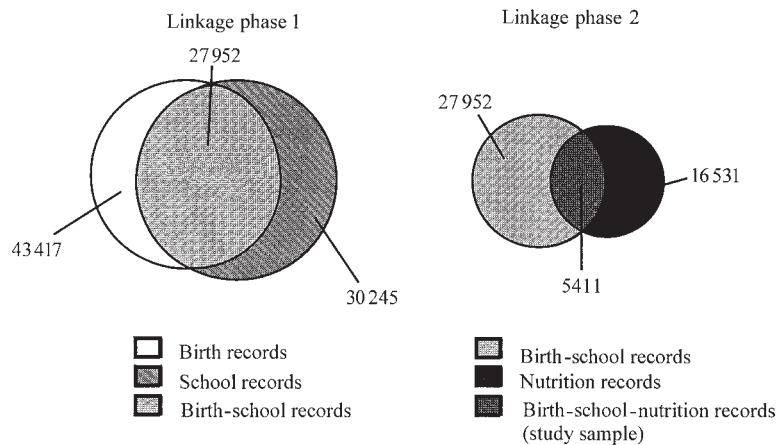
FIGURE 1. Description of the data linkage.

TABLE 1
Study variables and definitions, data sources, and prevalences (or means)

Variable and definition	Source	Prevalence or mean
Hemoglobin (g/L)	Nutrition record	115.6 ± 13.3[1]
Birth weight (%)	Birth record	
Very low (<1500 g)		1.1
Low (1500 to <2500 g)		8.6
Normal (≥2500 g)		90.3
Maternal education (%)	Birth record	
Low (<12 y)		48.6
Normal (12 y)		40.1
High (>12 y)		11.2
Male sex (%)	Birth record	47.2
Race-ethnicity (%)	Birth record	
Black		74.1
Hispanic		20.1
White		5.8
Age of mother (%)	Birth record	
(<18 y)		15.6
(18–35 y)		79.7
(>35 y)		4.6
Age of child at entry into the WIC program (mo)[2]	Nutrition record	13.13 ± 10.41
Mild or moderate mental retardation (%)[3]	School record	2

[1] $\overline{x} \pm$ SD.
[2] WIC, Special Supplemental Program for Women, Infants, and Children.
[3] Defined as educable or trainable mentally handicapped.

TABLE 2
Regression coefficients and adjusted odds ratios for the association between risk factors and mild or moderate mental retardation[1]

Variable	Odds ratio (95% CI)
Hemoglobin (g/L)	1.28[2] (1.05, 1.60)
Birth weight	
Very low	4.58[2] (1.04, 20.12)
Low	2.50[3] (1.36, 4.61)
Maternal education	
Low	11.94[2] (1.63, 88.08)
Normal	8.32[2] (1.12, 62.0)
Male sex	2.17[3] (1.33, 3.53)
Race or ethnicity	
Hispanic	0.39 (0.12, 1.22)
Black	0.79 (0.31, 2.02)
Age of mother	
18–35 y	2.51[2] (1.11, 5.69)
>35 y	4.27[2] (1.38, 13.2)
Age of child at entry into the WIC program (in mo)	1.03[3] (1.01, 1.05)

[1] Referent groups were as follows: normal birth weight, high maternal education, female sex, white race, and age of mother <18 y.
[2] $P < 0.05$.
[3] $P < 0.01$.

entry into the WIC program. This was defined as the earliest visit date for each child regardless of the clinic the child visited and regardless of whether that child was treated by the program. The children's ages at the time of the first visit ranged from 0 to 58.3 mo ($\overline{x} \pm$ SD: 12.7 $\pm$ 10.6 mo).

Birth weight, maternal education, sex, race-ethnicity, and age of mother were entered as categorical variables; simple contrasts were used. The referent groups were the lowest risk groups: normal birth weight, >12 y of education, female, white, and maternal age <18 y, respectively.

The analyses compared children with mild or moderate mental retardation with those who were achieving normally; 736 children with other types of special education placement, such as sensory handicaps or physical handicaps, were not included. Additionally, 60 children for whom maternal education data were missing and 848 children for whom hemoglobin concentrations were missing were excluded from the analyses. Complete data were available for 3771 children.

RESULTS

Preliminary analyses

A preliminary analysis of the demographic makeup of the linkage populations showed that the linked study sample (birth-school-nutrition) was significantly different from the birth-school sample for several variables, differences that were expected because the WIC program serves low-income families. The study sample had a higher percentage of children with educational disabilities, a higher percentage of black subjects, and lower means for birth weight, gestational age at birth, maternal education level, and maternal age than did the birth-school population. Compared with the unlinked nutrition only population,

the study sample differed in 2 variables: percentage of black subjects and percentage of children with low hemoglobin concentrations, both of which were lower in the study sample (22). The sample population was therefore demographically different from children identified by the birth-school linkage or by the nutrition only records. A statistical comparison of the mean hemoglobin concentration of the sample population with that of the overall population by z score was significant. However, the differences were slight; the sample parameters ($\overline{x} \pm$ SD: 115.6 $\pm$ 13.3 g/L) were generally similar to the population parameters ($\mu = 116.0$, $\sigma = 14.3$ g/L).

Outcome analyses

The effects of hemoglobin concentration, birth weight, maternal education, sex, race-ethnicity, age of mother, and age of child at entry into the WIC program on mild or moderate mental retardation are reported in **Table 2**. The effect of hemoglobin was significant after all covariates were entered into the equation [odds ratio (OR): 1.28; 95% CI: 1.05, 1.60]. Therefore, for each decrement in hemoglobin, risk of mild or moderate mental retardation increased by 1.28, even after we controlled for all other variables in the equation.

Children of mothers with low education and children of mothers with normal education were 11.94 and 8.32 times as likely, respectively, to be classified as mildly or moderately retarded as children of mothers with high education. Children with very low birth weights and those with low birth weights were 4.58 and 2.50 times as likely, respectively, to be classified as mildly or moderately retarded as children with normal birth weights. Males were 2.17 times more likely to be classified as mildly or moderately retarded than were females. Children of mothers aged 18–35 y were 2.51 times as likely to be classified as mildly or moderately retarded and children of mothers aged >35 y were 4.27 times as likely as children of mothers <18 y old. In addition, the older the child at entry into the WIC program, the more likely that child would be placed in special education for mild or moderate mental retardation.

DISCUSSION

Our findings support the position that iron deficiency, as reflected by restricted hemoglobin production, is significantly associated with mild or moderate mental retardation. The effect of iron deficiency persists in a low socioeconomic population, even after the effects of birth weight, maternal education, sex, race-ethnicity, age of mother, and age of child at entry into the WIC program are controlled for. These findings indicate that the risk of mild or moderate mental retardation increases with the severity of the anemia.

There are several implications of these findings.

1) Alleviating iron deficiency during early childhood may help to reduce the burden of educational disability in later childhood.
2) Efforts aimed at alleviating iron deficiency in the population, such as the WIC program, may have long-term benefits.
3) Long-term academic achievement and cost of special education services are important considerations in the study of the effects of iron deficiency.

Generalizations of the results beyond the WIC population must be made with caution. As expected, the results from the preliminary analyses in a previous study (22) comparing the linked data set with the unlinked data sets indicated differences among the linked populations. Because the analyses were computed with data on the WIC population in Dade County, which is demographically different from the general population, the results may not be generalizable beyond the sample population. The study sample was generally more at risk of detrimental outcomes than was the general population in Dade County. The results indicate that there is a significant association between iron deficiency and mild or moderate mental retardation in a high-risk sample. The size of the effect may be different in a lower-risk sample.

Our findings can be used to show an association between early childhood iron concentrations and development but are not proof of causality. To discuss whether low hemoglobin concentrations affect cognition directly, one must speculate and this speculation often evokes controversy (23, 24). The method that we used allowed us to assume that there is an association between the risk factor (in this case, iron concentrations) and the outcome (in this case, placement in educable or trainable mentally handicapped special education). The evidence presented here indicates that cognitive consequences of severe iron deficiency theoretically might be alleviated with treatment and prevention of severe iron deficiency during infancy and early childhood. The observed relation provides support for a causal argument. However, to conclusively establish causality, one would have to design an experiment in which iron-deficient infants and children were randomly assigned to treatment groups, an alternative that was not possible to investigate by using the archival data set available for the present study.

Some intervening variable may be causing the detrimental outcome. For example, iron-deficient children may be more susceptible to lead poisoning (25), which may produce some of the same adverse effects as iron deficiency (26). However, epidemiologic studies of lead toxicity have shown that lead concentrations in children in south Florida are low (27). Differences in the response to iron therapy may be due to unrelated medical conditions (28) or vitamin A deficiency (29). Low birth weight may be an indicator for maternal malnutrition, which in turn may also have a role in infant malnutrition, iron deficiency, and cognitive development (30).

Other environmental factors working or occurring together may also be responsible for effects on a child's development. As in previous studies, the risk factors of low birth weight, low maternal education, and male sex of the child provided significant additional risk for detrimental outcome (31). It is important to note the findings when the mothers' ages were examined. Teenage motherhood is often a risk factor for detrimental child outcome; however, in this WIC sample teenage mothers experienced the lowest risk. It is beyond the scope of the available data to analyze what factors contributed to this finding. One explanation may be in the eligibility criteria for the WIC program. Compared with older mothers, teenage mothers may meet the low-income requirement more easily with fewer additional risk characteristics. However, the finding may also be a statistical artifact because other risk factors such as low education that occur with maternal age were controlled for in the logistic regression (32).

Other studies have attempted to control for nutritional factors, socioeconomic status, low birth weight, and other environmental factors believed to be associated with behavioral development. According to a multisystems theory, these variables occur together naturally in the environment. Therefore, as these variables interact, it becomes increasingly difficult to determine their individual effects (33). Ecologically, these "control" variables coexist with iron deficiency and may be acting in concert with it against a child's optimal development. It is important to consider that studies that attempt to separate indicators of malnutrition, such as iron deficiency, from other types of environmental deprivation may be inappropriately separating factors that occur together naturally and that therefore cannot be differentiated. Intervention efforts may be most effective when targeted at children with multiple risk factors, including iron deficiency. The clear association that we found between degree of iron deficiency and a child's need for special education placement because of mild or moderate mental retardation supports efforts to provide proper nutrition to mothers, infants, and young children.

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