

## Early iron deficiency anemia and later mental retardation<sup>1,2</sup>

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The prevalence of iron deficiency anemia (IDA) has dropped significantly in the United States during the past 3 decades (1, 2). The third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) showed that for both sexes combined ( $n = 1339$ ) the prevalence of IDA was  $\leq 3\%$  for children aged 1–2 y and  $< 1\%$  for children aged 3–5 y. This decline was found among middle- and low-income children, although there was significant variability among minority groups, particularly among children  $< 2$  y of age (3–5). Prevalence rates for some low-income children in some states, however, are still much higher than those for the whole country (6). For example, in Solano and Alameda counties in northern California,  $\geq 30\%$  of children tested were determined to be anemic (P Scariati, unpublished observations, 1996). Because the anemia rates for these and other California counties were high, researchers from the Centers for Disease Control and Prevention recently evaluated the validity of the anemia data obtained in Alameda, Sacramento, and Fresno counties. There was evidence of measurement error within some of the clinics in these 3 counties, but anemia rates still appeared to be higher than the national average. In the United States, iron deficiency is the primary determinant of anemia.

Thus, if early anemia is a cause of mild or moderate mental retardation, then the problem of IDA still demands consistent public health attention as suggested by Hurtado et al (7) in this issue of the Journal. The epidemiologic evidence presented by Hurtado et al is compelling and agrees with 2 sets of findings published previously. IDA during the first 2 y of life was associated with poor performance on tests of intelligence or specific cognitive processes at or near school age in Israel, Costa Rica, and Chile (8). Also, with one exception (9), delays in mental development observed in infants and toddlers with IDA were not fully reversed after the children were treated with iron (10).

Dallman et al (11) showed that in rats given an iron-deficient diet from 10 to 28 or 48 d of age a deficiency of nonheme iron in the brain was not corrected after nutritional rehabilitation. Also, iron-deficient diets given to adolescent rats during gestation and lactation lowered the concentration of brain iron in pups at 3 mo of age (12). It is thus plausible that the associations between IDA and long-term intellectual deficits are mediated by either anatomic or neurochemical changes. More specifically, existing data point to changes in the dopaminergic system and hypomyelination (13, 14).

The information above strongly justifies the inclusion of IDA as a risk factor for determining eligibility for the Special Supplemental Program for Women, Infants, and Children (WIC) (15). However, the public health and scientific conclusions that

should be drawn from Hurtado et al's (7) data are not equivalent. Definitive conclusions from all information currently available regarding the long-term functional consequences of IDA or the irreversibility of the early functional alterations it produces are scientifically unwarranted. The study reported by Hurtado et al (7), based on a large data set ( $n = 5411$ ) that linked records from the WIC program with records from public schools in Dade County, FL, is illustrative. For each decrement in hemoglobin concentration (g/L), the risk of mild or moderate retardation increased (1.28) after several potential confounders were controlled for. Birth weight, maternal education, sex, and age of the mother also predicted anemia but the odds ratio in each of these cases was  $> 1.28$ .

The "early trauma later deficit" hypothesis has a long-standing history in developmental psychobiology, although most researchers fully recognize that caution must be exercised before drawing definitive conclusions because of the inherent problems of controlling for confounders. Controlled experimental trials that follow children with IDA from infancy to the school period are unethical and, therefore, unavailable. Based on their work, Lozoff et al (16) carefully pointed at the limitations of quasiexperimental longitudinal research regarding the long-term developmental consequences of early IDA. The authors noted the possibility that social environmental factors that remained untapped accounted for the cognitive differences observed at 5 y of age between children who did and did not have IDA in early life. IDA in the United States and elsewhere is more likely to occur among poor, minority children (6). Data generated by NHANES III show that lower-income, minority status and lower parental education are independently associated with lower scores on cognitive outcomes (17).


In the study in Dade County, FL (7), the problem of confounders is also tied to the outcomes. Mildly to moderately retarded children do not constitute a homogeneous group, etiologically or functionally. Besides genetic factors (eg, chromosomal and metabolic), multiple prenatal (eg, alcohol exposure and intrauterine growth retardation) and postnatal (eg, anoxia and homelessness) biological and socioeconomic factors cause learning disabilities and retardation (18). Learning disabilities and

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mental retardation represent either a general developmental lag or include several specific cognitive dysfunctions that, when combined, interfere with school progress and performance in most or all areas of learning. No existing data suggest that IDA interferes with several cognitive functions; in fact, the particular functions at highest risk remain unknown. Iron is not equally distributed in all regions of the brain and it is unlikely that IDA will equally affect all of the neural substrates of cognitive function (19, 20).

In light of the small effect estimated in Dade County, the issue of confounding, and the heterogeneity of the target population, the findings (7) should be interpreted cautiously. This study does, however, add useful information to the substantive body of data building on the role of IDA as a developmental risk factor. 

## REFERENCES

1. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA* 1997;277:973-6.
2. Committee on Iron Deficiency. Iron deficiency in the United States. *JAMA* 1968;203:119-24.
3. Yip R, Binkin NJ, Fleshood L, Trowbridge FL. Declining prevalence of anemia among low-income children in the United States. *JAMA* 1987;258:1619-23.
4. Yip R, Walsh KM, Goldfarb MG, Binkin NJ. Declining prevalence of anemia in childhood in a middle-class setting. *Pediatrics* 1987;80:330-4.
5. Sherry B, Bister D, Yip R. Continuation of decline in prevalence of anemia in low-income children: the Vermont experience. *Arch Pediatr Adolesc Med* 1997;151:928-30.
6. Yip R, Parvanta I, Scanlon K, Borland E, Russell C, Trowbridge F. Pediatric nutrition surveillance system—United States, 1980-1991. *MMWR Morb Mortal Wkly Rep* 1992;41(SS-7):1-24.
7. Hurtado EK, Claussen AH, Scott KG. Early childhood anemia and mild or moderate mental retardation. *Am J Clin Nutr* 1999;69:115-9.
8. Watkins WE, Pollitt E. Iron deficiency and cognition among school-age children. In: Dobbing J, ed. *Brain, behavior and iron in infant diet*. London: Springer Verlag, 1990:179-97.
9. Idjradinata P, Pollitt E. Reversal of developmental delays in iron-deficient anaemic infants treated with iron. *Lancet* 1993;341:1-4.
10. Lozoff B. Has iron deficiency been shown to cause altered behavior in infants? In: Dobbing J, ed. *Brain, behavior and iron in infant diet*. London: Springer Verlag, 1990:107-31.
11. Dallman PR, Siimes MA, Manies EC. Brain iron: persistent deficiency following short-term iron deprivation in the young rat. *Br J Haematol* 1975;31:209-15.
12. Felt BT, Lozoff B. Brain iron and behavior of rats are not normalized by treatment of iron deficiency anemia during early development. *J Nutr* 1996;126:693-701.
13. Nelson C, Erikson K, Pinero DJ, Beard JL. In vivo dopamine metabolism is altered in iron-deficient anemic rats. *J Nutr* 1997;127:2282-8.
14. Lozoff B. Explanatory mechanisms for poorer development in iron-deficient anemic infants. In: *Nutrition, health and child development. Research advances and policy recommendations*. Vol 566. Washington, DC: Pan American Health Organization, 1998:162-78.
15. Institute of Medicine. *WIC nutrition risk, criteria A scientific assessment*. Washington, DC: National Academy Press, 1996.
16. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. In: *Nutrition, health and child development. Research advances and policy recommendations*. Vol 566. Washington, DC: Pan American Health Organization, 1998:179-97.
17. Kramer RA, Allen L, Gergen PJ. Health and social characteristics and children's cognitive functioning: results from a national cohort. *Am J Public Health* 1995;85:2312-8.
18. Aicardi J. The etiology of developmental delay. *Semin Pediatr Neurol* 1998;5:15-20.
19. Hill JM. The distribution of iron in the brain. In: Youdim MBH, ed. *Brain iron neurochemistry and behavioural aspects*. London: Taylor & Francis, 1989:1-24.
20. Hill JM. Comments. *Am J Clin Nutr* 1989;50(suppl):616-7.