Double Burden of Iron Deficiency in Infancy and Low Socioeconomic Status

A Longitudinal Analysis of Cognitive Test Scores to Age 19 Years

Betsy Lozoff, MD; Elias Jimenez, MD; Julia B. Smith, EdD

Objective: To assess change in cognitive functioning after iron deficiency in infancy, depending on socioeconomic status (SES; middle vs low).

Design: Longitudinal study.

Setting: Urban community in Costa Rica (infancy phase [July 26, 1983, through February 28, 1985] through 19-year follow-up [March 19, 2000, through November 4, 2002]).

Participants: A total of 185 individuals enrolled at 12 to 23 months of age (no preterm or low-birth-weight infants or infants with acute or chronic health problems). The participants were assessed in infancy and at 5, 11 to 14, 15 to 18, and 19 years of age. A total of 97% were evaluated at 5 or 11 to 14 years and 78% at 15 to 18 or 19 years. Individuals who had chronic iron deficiency in infancy (iron deficiency with hemoglobin concentrations ≤10.0 g/dL or, with higher hemoglobin concentrations, not fully corrected within 3 months of iron therapy) were compared with those who had good iron status as infants (hemoglobin concentrations ≥12.0 g/dL and normal iron measures before and/or after therapy).

Main Outcome Measures: Cognitive change over time (composite of standardized scores at each age).

Results: For middle-SES participants, scores averaged 101.2 in the group with chronic iron deficiency vs 109.3 in the group with good iron status in infancy and remained 8 to 9 points lower through 19 years (95% confidence interval [CI], –10.1 to –6.2). For low-SES participants, the gap widened from 10 points (93.1 vs 102.8; 95% CI for difference, –12.8 to –6.6) to 25 points (70.4 vs 95.3; 95% CI for difference, 20.6 to 29.4).

Conclusions: The group with chronic iron deficiency in infancy did not catch up to the group with good iron status in cognitive scores over time. There was a widening gap for those in low-SES families. The results suggest the value of preventing iron deficiency in infancy.

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Author Affiliations: Center for Human Growth and Development and Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor (Dr Lozoff); Department of Hematology, Hospital Nacional de Niños, San Jose, Costa Rica (Dr Jimenez); and Department of Educational Leadership, Oakland University, Rochester, Mich (Dr Smith). Dr Jimenez is currently with the Department of Pediatrics, Hospital CIMA San Jose, San Jose, Costa Rica.

I NFANTS WITH IRON DEFICIENCY anemia or other indications of chronic, severe iron deficiency have shown lower cognitive test scores than infants with good iron status in all but 1 of 14 studies that assessed overall cognitive functioning, from countries around the world.[1,2] The few available follow-up studies at school age or early adolescence report persisting lower scores despite iron therapy in infancy.[3-7] A recent meta-analysis estimated the long-term effects on IQ to be 1.73 points lower for each 1.0-g/dL decrease in hemoglobin.[8] Differences in group means raise questions about stability and change over time. Is there evidence of catch-up or further decline? Does the impact of iron deficiency in infancy vary over time depending on socioeconomic circumstances? These issues pertain to millions of children.[8] An estimated 20% to 25% of infants worldwide have iron deficiency anemia, and more have iron deficiency without anemia.[9-11] Poor, minority, and/or immigrant infants in industrialized countries are also at increased risk for iron deficiency.[12]

To address questions about change over time depending on iron status in infancy and socioeconomic status (SES), we applied techniques of longitudinal analysis[13] to data from an ongoing study in Costa Rica. Previous cross-sectional analyses showed that cognitive test scores for the group with chronic, severe iron deficiency in infancy (see the "Methods" section) were lower than the group with good iron status in infancy[14] and at ages 5 and 11 to 14 years.[6,15] By 11 to 14 years, a higher proportion of children in the group with chronic iron deficiency had repeated a grade in school and/or been referred for special services.[6] The present study assessed change in cognitive test performance from the second year of life to the transition to adulthood (19 years) according to SES.

METHODS

SAMPLE

The analysis used data from a longitudinal study in Costa Rica that included evaluations in infancy and 4 subsequent follow-ups (5, 11-14, 15-18, and 19 years of age). Enrollment in the original infant study was conducted from July 26, 1983, through February 28, 1985, in an urban community near San Jose, the capital of Costa Rica.[14] The 19-year evaluation was conducted from March 19, 2000, through November 4, 2002. The community was mixed middle and lower class, and parents of study infants averaged 8 to 10 years of education. Enrollment entailed door-to-door screening, inviting study participation for all 12- to 23-month-old infants who had a birth weight of 2.5 kg or higher and a singleton, full-term, uncomplicated birth who were free of acute or chronic medical problems and had normal physical examination results. The refusal rate was 11.6%. Infants enrolled in the study had no evidence of growth failure or other nutrient deficiencies.[14] The mean age at study entry was 17 months. Iron deficiency was thus likely to have lasted for months, especially since the local feeding practice at the time was to introduce unmodified cow's milk in the first months of life (along with breastfeeding). Of the 191 infants in the initial study, 185 provided data for this longitudinal analysis (6 were excluded because of lack of information about their iron status after iron therapy).

Figure 1 shows a flowchart of the number and percentage of participants at each subsequent assessment. From the 5-year follow-up study,[15] 161 children provided data for the longitudinal analysis. All but 15 received the comprehensive psychoeducational assessment within 2 weeks of their fifth birthday (age range, 59-63 months). From the reevaluation at age 11 to 14 years,[6] 162 children provided data (mean age, 12.3 years; range, 10.9-13.7 years). Overall, 97% of the original sample participated in assessments either at age 5 years or early adolescence. A brief follow-up in late adolescence provided data for 133 participants (mean age, 16.4 years; range, 15.0-17.9 years). A comprehensive assessment at 19 years provided data for 121 participants (mean age, 19.0 years; range, 18.0-20.0 years). A total of 145 (78%) of the original 185 participants were evaluated at 15 to 18 years and/or 19 years. Participants who were not tested at a given age often participated subsequently (Figure 1). Lack of participation was primarily due to difficulty in locating a family.

Parental signed informed consent for each phase of the study was obtained by the project pediatrician. Assent or consent of the adolescent was obtained beginning with the early-adolescent follow-up. The infancy and 5-year protocols were approved by the institutional review board of Case Western Reserve University, Cleveland, Ohio, and subsequent protocols were approved by the institutional review board of the University of Michigan. All protocols were approved by ethics committees of the Hospital Nacional de Niños or Instituto Costarricense de Investigationes Clinicas (for the 19-year evaluation) and the Ministry of Health, San Jose, Costa Rica.

MEASURES

Iron Status

Iron status in infancy was determined by venous concentrations of hemoglobin, transferrin saturation, free erythrocyte protoporphyrin, and serum ferritin. Iron deficiency was defined as 2 or more abnormal iron measures (a serum ferritin concentration of <12 ng/mL [<27.0 pmol/L] and either a free erythrocyte protoporphyrin level of ≥100 µg/dL [≥1.77 µmol/L] of red blood cells or a transferrin saturation of <10%)."[16-18] Iron suf-
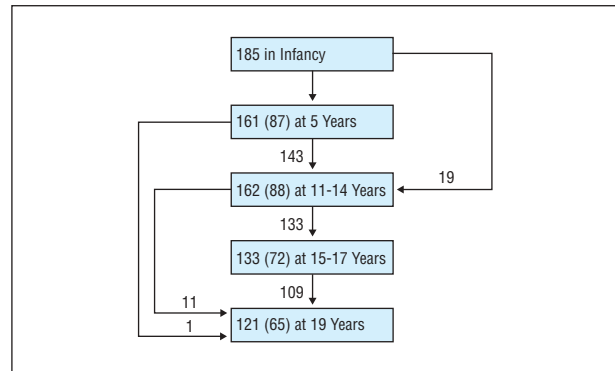

Figure 1. Flowchart of study participation. The number (percentage) of participants at each time point is shown, indicating that participants who missed an assessment were often available subsequently. Numbers between boxes indicate number of children studied at both ages in connected boxes. Numbers by outer arrows are children who missed 1 or more assessments but were evaluated at the ages shown.

ficiency was defined as a hemoglobin concentration of 12.0 g/dL or more and normal values on all iron status measures. Hematologic response to iron therapy in infancy was excellent, with a mean hemoglobin increase of 3.7 g/dL among iron-deficient infants with a hemoglobin concentration of 10.5 g/dL or less. Anemia in all infants resolved following 3 months of iron therapy, but as might be expected, those with indications of more severe or chronic iron deficiency still had biochemical alterations, such as elevated erythrocyte protoporphyrin values.[14] At the subsequent follow-ups that included blood collection (5, 11-14, and 19 years),[6,15] iron deficiency was present in less than 5%, and no one had iron deficiency anemia except for 4 women at 19 years, 2 of whom were pregnant. These data indicate that the Costa Rican diet at the time provided adequate iron to correct any iron parameters that were still altered after treatment in infancy and to maintain good iron status thereafter.

Following the approach in the 5-year follow-up and subsequent reports,[6,15,19] we compared participants who had chronic, severe iron deficiency in infancy (with or without anemia) with the rest of the sample who were iron sufficient before and/or after iron therapy in infancy. For simplicity, the chronic, severe iron-deficient group will be referred to as "chronic iron deficiency" and the rest of the sample as "good iron status." The chronic–iron deficiency group consisted of participants who had marked iron deficiency anemia in infancy (hemoglobin ≤10.0 g/dL) and those with higher hemoglobin concentrations and iron deficiency that did not fully correct after 3 months of iron therapy.[15] Analyses compared the chronic–iron deficiency (n=53) and good–iron status (n=132) groups. There was no differential attrition; the chronic–iron deficiency group constituted 28% to 29% of the sample in both infancy and the late-adolescent follow-up.

Cognitive Assessments

In infancy, the Mental Development Index of the Bayley Scales of Infant Development[20] was administered before and after iron treatment. At the 5-year follow-up, the overall tests of cognitive function were the Wechsler Preschool and Primary Scale of Intelligence[21] and the Woodcock-Johnson Psychoeducational Battery.[22] At 11 to 14 years, the general cognitive measures were the Wechsler Intelligence Scale for Children–Revised,[23] the Wide Range Achievement Test–Revised (arithmetic and reading),[24] and the Directed Writing Task.[25] At 15 to 18 years, the measures were arithmetic and reading achievement[24] and the Directed Writing Task.[25] At 19 years, the gen-

eral cognitive measures were arithmetic achievement[24] and 5 subscales of the Wechsler Intelligence Scale for Adults,[26] prorated to estimate verbal and performance intelligence scores.[27] All assessments were conducted by trained Costa Rican psychologists who were unaware of participants' hematologic status at any age.

Factor analyses (principal components with Varimax rotation[28]) showed that the general cognitive measures at each assessment were closely associated with each other. Each set of measures yielded a single factor that explained 62% (5 years) to 78% (19 years) of the variance. This data reduction information warranted combining measures into a composite cognitive score for a given age. Since all tests were standardized or could be rescaled to a mean of 100 and an SD of 15 to 16, analyses could be conducted across ages and differing tests. In the longitudinal model structure described herein, all analyses were adjusted for each individual's exact age at each follow-up. Results report change relative to age-normed scores based on US standardization samples at each time point. Thus, a "decline" is relative to norms for age, rather than in actual knowledge or absolute cognitive performance.

Environmental Factors

Iron deficiency often goes along with other individual, family, and/or environmental disadvantages, some of which could affect cognitive development.[1,29-31] The critical comparison of our study considers the impact of infant iron status depending on family SES. Measures of family SES generally assess such factors as family structure, economic circumstances, education, and occupation. We used the Hollingshead Four Factor Index,[32] which considers parental education and occupation and father presence and is widely used. We compared individuals whose family SES in infancy was low (levels 4 and 5: unskilled and semiskilled workers) or middle to high (levels 1-3: professional, managerial, clerical, and skilled workers).[32]

STATISTICAL ANALYSIS

Longitudinal analysis using hierarchical linear modeling (HLM) was the primary statistical approach.[13,33] This class of analytic techniques has not previously been applied to change in cognitive scores over time with iron deficiency in infancy. By considering the within-individual correlations between measures, longitudinal analysis provides relatively unbiased estimates for each individual of the starting level (intercept), change over time (slope), and acceleration or deceleration (curvature). The study's analyses were conducted with HLM software.[33] Hierarchical linear modeling estimates the covariance structure appropriately in data sets that, like ours, have incomplete and unbalanced time parameters, with a varying number of assessments and intervals between assessments for different individuals, resulting in a varying variance structure.[13] The analysis used measures nested within individuals (level 1), comparing differences between individuals in the good–iron status and chronic–iron deficiency groups (level 2). The level 1 model used individual age at testing as the time parameter, with the change estimated specific to the amount of time between assessments for each individual. We tested for the possibility of curvilinear components or multiple growth trajectories, as well as single linear change, and selected the most parsimonious and best-fitting model based on the lowest deviance relative to the *df*.[13] The best model estimated 2 distinct slopes: one for change from infancy to age 5 years and another for change from 5 to 19 years of age. Models were anchored to actual test scores at the beginning and end of these intervals (infancy, age 5 years, and age 19 years).

We tested for an interaction between iron status in infancy and SES (middle vs low) in an overall model. The interactions were statistically significant for intercept (*P*=.02) and both slopes (*P*=.003 for change from infancy to age 5 years and *P*=.01 for change from age 5 to 19 years). To facilitate interpretation, we present results comparing change over time in the chronic–iron deficiency and good–iron status groups separately for middle- and low-SES families (for middle-SES families, 67 had good iron status and 20 had chronic iron deficiency; for low-SES families, 65 had good iron status and 33 had chronic iron deficiency). The estimated intercepts and change over time for these analyses match the estimates from the overall model. Where appropriate, we conducted post hoc tests of common parameters for significant differences by examining the difference in parameter estimate relative to the pooled SE of the estimate (a form of *t* test comparison).[13]

RESULTS

A higher proportion of the chronic–iron deficiency group was male (75% vs 48% in the good–iron status group; *P*=.005), as noted in previous reports.[6,14] These individuals also weighed 200 g less at birth (mean [SD] birth weight: 3.1 [0.3] kg vs 3.3 [0.4] kg in the good–iron status group; *P*=.02). Sex and birth weight were therefore covaried in all analyses. The sample was reasonably balanced between middle- and low-SES families (87 middle-SES families and 98 low-SES families). Socioeconomic status was lower in the chronic–iron deficiency group when analyzed as a continuous variable (mean [SD] Hollingshead score: 27.2 [10.8] vs 31.0 [12.6] in the good–iron status group; *P*=.02). However, the difference in the proportion in low-SES families did not reach statistical significance. Sixty-two percent of the chronic–iron deficiency group came from low-SES families compared with 49% of the good–iron status group (*P*=.11).

Figure 2 shows the relationship between iron deficiency and cognitive test scores over time depending on SES. In middle-SES families, initial cognitive scores for participants who had chronic iron deficiency in infancy averaged 8 points lower than those with good iron status (101.2 vs 109.3; difference in infancy, –8.15; 95% CI, –10.1 to –6.2; effect size, 0.54 SD). No statistically significant differences were found between groups in change from infancy to age 5 years or from 5 to 19 years of age. Thus, the magnitude of difference was maintained; at 19 years, their scores averaged 9 points lower (98.2 vs 107.6; 95% CI for the difference, –11.0 to –7.0).

In low-SES families, initial cognitive scores for participants with chronic iron deficiency in infancy averaged 10 points lower than those with good iron status (93.1 vs 102.8; difference in infancy, –9.7; 95% CI, –12.8 to –6.6; effect size, 0.67 SD). Scores for the chronic–iron deficiency group declined from infancy to age 5 years (difference in rate of change, –1.8; 95% CI, –2.6 to –1.1), whereas those for the good–iron status group did not. Although a pattern of decline in cognitive test scores from 5 to 19 years was generally observed, in low-SES families, the decline among individuals with chronic iron deficiency in infancy was steeper than for those in the good–iron status group (difference in rate of change, –0.6; 95% CI, –0.8 to –0.3). This resulted in mean scores of 70.4 vs 95.3 by 19 years—a 25-point gap (95% CI, 20.6 to 29.4;

effect size, 1.67 SD)—between chronic–iron deficiency and good–iron status groups with low-SES backgrounds.

In light of our interest in environmental disadvantage, we also compared iron status groups across SES levels in a post hoc comparison of models. For the good–iron status group, those in low-SES families had scores in infancy 7 points (95% CI, 4.0 to 10.0; effect size, 0.47 SD) lower than those in middle-SES families, increasing to 12 points (95% CI, 8.4 to 15.6) by age 19 years. For the chronic–iron deficiency group, individuals from middle-SES families started with scores in infancy like those of the good–iron status group in low-SES families: in between those with good iron status from middle-SES families and those with chronic iron deficiency from low-SES families. The chronic–iron deficiency group from middle-SES families showed a pattern over time like that of the good–iron status group in middle-SES families except 8 to 9 points lower (95% CI, 5.2 to 11.8; effect sizes, 0.53 to 0.60 SD). In contrast, the cognitive test score gap for individuals in the chronic–iron deficiency group from low-SES families (compared with those in middle-SES families) widened from 8 points (95% CI, 5.4 to 10.8) in infancy to 28 points at age 19 years (95% CI, 23.6 to 32.4; effect size, 1.87 SD).
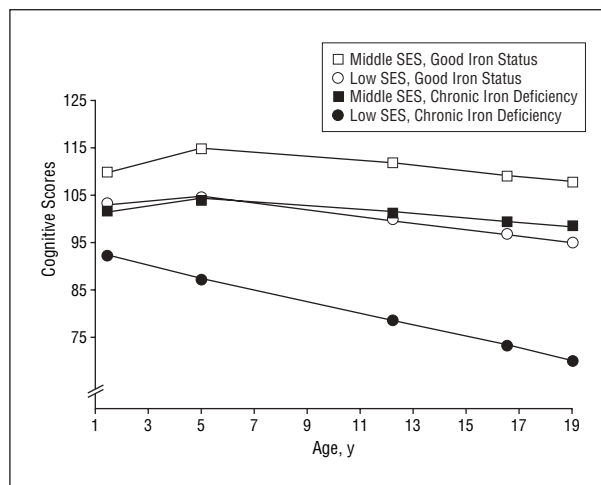

Figure 2. Cognitive composite scores over time, comparing infant iron status groups within middle- and low-socioeconomic status (SES) families. Iron status group and SES level each affected initial scores (*P*=.01 for chronic–iron deficiency difference within middle-SES families and *P*=.003 for chronic–iron deficiency difference within low-SES families). Change over time differed only for the chronic–iron deficiency group in low-SES families (*P*=.02 for change from infancy to age 5 years and *P*=.04 for change from age 5 to 19 years). Each participant is represented once: good iron status (n=67) compared with chronic iron deficiency (n=20) in middle-SES families and good iron status (n=65) compared with chronic iron deficiency (n=33) in low-SES families. Symbols are placed at the average age for each assessment.

COMMENT

Using longitudinal analytic techniques, this study showed no evidence of catch-up in cognitive test performance for individuals with chronic iron deficiency in infancy and a widening gap for those in low-SES families. This finding was observed despite iron therapy in infancy sufficient to correct anemia for those who had been anemic and good iron status thereafter. A gap of the observed magnitude (25-28 points) is likely to correspond to major differences in life course.

The observed pattern appears to make sense in terms of the cumulative and transactional nature of cognitive development.[34-36] Acquisition of new skills is intimately linked to mastery of skills at an earlier developmental level. If direct and indirect effects of early iron deficiency on the brain[37] disrupted or delayed basic developmental processes, there could be a snowball effect. In an economically stressed family environment, there might not be the resources or capacity to help children compensate. Together, these factors could contribute to earlier school failure[6] and less advanced cognitive processes in individuals with chronic iron deficiency in infancy in low-SES families. Thus, our results fit with the concept of "double jeopardy" or "double hazard"[38,39] (ie, worse outcome among individuals who experience both an early biological insult or stressor and more disadvantaged background[40]).

As expected, individuals from disadvantaged backgrounds showed lower cognitive test scores. This was confirmed for both the good–iron status and chronic–iron deficiency groups. Even with good iron status in infancy, low-SES individuals showed a decline in test scores like that observed in the United States.[41] Our observation that SES differences in cognitive test performance appeared to be set by preschool age and not improved

by schooling has also been reported in the United States and elsewhere.[42,43] This has sometimes been called the Matthew effect[44,45] in reference to the biblical quotation "To all those who have, more will be given, and they will have an abundance, but from those who have nothing, even what they have will be taken away." However, there was a differential effect of iron status on change over time in low-SES families. Individuals in the chronic–iron deficiency group not only tested lower in infancy but also showed a more marked decline, and hence an increasing gap, in subsequent cognitive test performance. Thus, good iron status before and/or after iron therapy in infancy appeared to attenuate the decline.

A major food supplementation trial in Guatemala found that early nutritional supplementation eliminated the decline in test scores associated with low SES.[46] Although the interventions differed (single micronutrient in our study and energy plus multimicronutrients in the Guatemala study), both studies provide support for long-term cognitive benefits of improved nutrition in infancy. Several investigators have assessed the likelihood that improved nutrition contributes to the rising IQs observed in many countries.[47] IQ tests and other such measures have had to be restandardized to adjust for rising scores. Because infant iron status has improved markedly in the United States and elsewhere in the past several decades,[48,49] a reduction in iron deficiency might play a role in the continued phenomenon of rising IQs. If the pattern we observed among individuals with good iron status before or after iron therapy in infancy applies elsewhere (ie, higher cognitive test scores later on), there might be corresponding population-level increases in cognitive test scores with improved iron status in infancy. If replicated, the results would suggest that even in the

face of stressed economic conditions, improving infant iron status has the potential for major societal impact in countries where iron deficiency is widespread.

The results should be interpreted in the context of the study's limitations. When the study started in 1981, few tests of specific cognitive functions in 1- to 2-year-old infants were available, and the only early cognitive measure was the Mental Development Index of the Bayley Scales of Infant Development. Consequently, this longitudinal analysis cannot provide evidence of specific central nervous system effects of early iron deficiency. The study also cannot determine the duration of iron deficiency; it could have started in the first year or even earlier (prenatally). The study is further limited by its small sample size and potential confounding by measured and unmeasured factors. Although missing data could also bias the results, losses were relatively low, considering follow-up from infancy to the transition to adulthood.

Socioeconomic status may exert its effects in different ways in various societies and cultures. Thus, the relationships observed in this Costa Rican sample may not generalize to other parts of the world. Furthermore, study participants were full-term infants, free of chronic or acute illnesses, and growing normally by US standards. Children who are not in such good overall health might not show the same effects. Conversely, children who experience briefer or milder iron deficiency in infancy might not show the pattern of declining cognitive test scores we observed. However, most infants in the world are not tested for anemia or iron deficiency and thus may experience even more prolonged or severe and/or untreated iron deficiency. Their outcome might be poorer than what we observed.

CONCLUSIONS

In this study in Costa Rica, participants who had chronic, severe iron deficiency in infancy (moderate iron deficiency anemia or hemoglobin concentrations >100 g/L with abnormal iron measures after treatment) did not catch up in cognitive test scores over time to those who were iron sufficient before and/or after treatment in infancy. For individuals from middle-SES families who had chronic iron deficiency in infancy, the magnitude of the gap remained the same from infancy to age 19 years (8-9 points lower). However, those in lower-SES families seemed doubly burdened; the gap widened substantially from 10 points in infancy to 25 points at age 19 years. Such a difference is likely to be functionally significant regarding educational attainment and career choices in adulthood. The analysis also suggested a protective effect of good iron status in infancy in low-SES families. In light of potential adverse effects at the level of the individual and the society in settings where iron deficiency is widespread, it seems reasonable to prevent iron deficiency in infancy and treat it before it becomes chronic or severe.

Correspondence: Betsy Lozoff, MD, Center for Human Growth and Development, 300 N Ingalls, University of Michigan, Ann Arbor, MI 48109-0406 (blozoff@umich.edu).

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There are few experiences more deeply disturbing for the inexperienced mother than the sight of her child in the grip of some unexplained illness.

—From *A Parent's Guide to Children's Illnesses*, by Dr John Henderson, 1957