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Effects of iron deficiency in infancy on patterns of motor development over time

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Abstract

This longitudinal study of the effects of iron deficiency in infancy assessed motor development over time in 185 healthy Costa Rican children who varied in iron status at 12–23 months. Longitudinal analyses (hierarchical linear modeling) used the Bayley Psychomotor Index before and both 1 week and 3 months after iron treatment in infancy and the Bruninks-Oseretsky Test of Motor Proficiency – long form at 5 years and short form at 11–14 years. Children with chronic severe iron deficiency in infancy had lower motor scores at the beginning of the study and a lower but parallel trajectory for motor scores through early adolescence. Thus, there was no evidence of catch-up in motor development, despite iron therapy in infancy that corrected iron deficiency anemia in all cases.

Keywords

Motor development; Iron deficiency; Longitudinal; Human; Infant

1. Introduction

There is renewed interest in the relationship between nutritional deficiencies in infancy and motor development (Kariger et al., 2005; Kuklina, Ramakrishnan, Stein, Barnhart, & Martorell, 2004; Pollitt, 2000a). Although most previous studies on early nutritional deficiencies emphasize cognitive effects, the impact on motor development may be no less important. Adequate motor development is necessary for adequate visual-perceptual and cognitive development in infancy. Locomotion enables the infant to reach new objects and new places, opening opportunities for exploration, and has been shown to be critical for the development of visual perception (Adolph, Eppler, & Gibson, 1993a, 1993b) and spatial orientation (Acredolo, 1990). Sufficient fine motor control is required for effective object manipulation, through which infants develop their capabilities to process perceptual information. Indeed, a conceptual multi-level model of long-lasting intellectual delays in undernourished infants, developed by Pollitt and colleagues, postulates that poorer motor development is one of the first-level variables influencing cognitive outcome (Pollitt, 2000a; Pollitt, Jahari, & Walka, 2000; Walka & Pollitt, 2000).

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Motor development also influences the infant's independence and self-care, which can affect social-emotional attributes such as confidence and self-esteem. It has been shown, for example, that walking without assistance is followed by emotional changes reflecting autonomy and assertiveness and that infants become more sociable and affectionate after acquisition of walking skills (Biringen, Emde, Campos, & Appelbaum, 1995; Campos, Kermoian, & Zumbahlen, 1992). Sufficient motor abilities are also important for adequate development of social skills during early childhood as children socialize through play. In early childhood, play is based mostly on interactions through and during physical activity. Furthermore, motor development during childhood may provide the foundation for subsequent development of occupational performance in adulthood and ability to enjoy and participate in social leisure activities that involve motor skills (e.g., sports, dancing, etc.).

This study focused on iron deficiency (ID), the most common nutrient deficiency in the world. In developing countries 46–66% of children under four years are anemic, with half attributed to ID (Stoltzfus, Mullany, & Black, 2004). A number of studies have reported lower motor development scores for infants with IDA or other indication of chronic severe ID, compared to infants with good iron status. Thirteen such studies from countries around the world assessed otherwise healthy 6- to 24-month-old infants using a standardized motor test (Akman et al., 2004; Antunes, 2004; Driva, Kafatos, & Salman, 1985; Hasanbegovic & Sabanovic, 2004; Hokama, Gushi, & Nosoko, 2005; Idjradinata & Pollitt, 1993; Johnson & McGowan, 1983; Lozoff, Brittenham, Viteri, Wolf, & Urrutia, 1982; Lozoff et al., 1987; Lozoff, Wolf, & Jimenez, 1996; Shafir Liberzon et al., 2005; Walter, De Andraca, Chadud, & Perales, 1989; Walter, Kovalskys, & Stekel, 1983). Eight of them found IDA infants to have lower motor scores (Akman et al., 2004; Hasanbegovic & Sabanovic, 2004; Hokama et al., 2005; Idjradinata & Pollitt, 1993; Lozoff et al., 1982, 1987; Shafir Liberzon et al., 2005; Walter et al., 1989). In addition, in a British population study, low hemoglobin (Hb) concentration (≤ 95 g/L) in 8-month-old infants was associated with poorer motor development at 18 months (Sheriff, Emond, Bell, Golding, & Alspac, 2001). Similarly, IDA infants at risk for stunting showed poorer motor development. For instance, IDA infants walked later in two recent studies in Nepal and Zanzibar (Kariger et al., 2005; Siegel et al., 2005).

Several of these studies sought to demonstrate an effect of ID on motor development by showing improvement after a full course of iron therapy (≥ 3 months). Seven studies used standardized tests and are sufficiently similar for comparison (Akman et al., 2004; Antunes, 2004; Hasanbegovic & Sabanovic, 2004; Idjradinata & Pollitt, 1993; Lozoff et al., 1987, 1996; Walter et al., 1989). Four reported that lower motor scores persisted in IDA infants (Hasanbegovic & Sabanovic, 2004; Lozoff et al., 1987, 1996; Walter et al., 1989), whereas the other three observed improvements (Akman et al., 2004; Antunes, 2004; Idjradinata & Pollitt, 1993). Although the reasons for the differing results are still unknown, pretreatment scores were much lower in IDA infants in the studies that showed improvement, compared to those that did not.

There are also 10 randomized controlled trials of iron supplementation (or placebo), regardless of initial iron status. Among preventive trials with healthy full-term infants in the 6–24 month range, one in Canada showed lower motor scores at 9 and/or 12 months in the group that did not receive prophylactic iron (Moffatt, Longstaffe, Besant, & Dureski, 1994). A large study in Chile ($n = 1657$) found that infants who did not receive iron crawled somewhat later and more were rated as tremulous (Lozoff et al., 2003). A small randomized controlled trial involving breast-fed infants in Canada showed a benefit of even earlier iron supplementation. Infants who received iron between 1 and 6 months had better motor scores at 12 months, compared to those receiving placebo (Friel et al., 2003). Two preventive trials with healthy term infants did not show motor effects (Morley, Abbott, Fairweather-Tait, MacFayden, & Sterman, 1999; Williams et al., 1999).

In addition to the Chile study, there are four other large, recent supplementation trials in developing countries. They involved infants at risk for stunting (Black et al., 2004, 2002; Lind et al., 2004) often assessing iron with or without other micronutrients. All showed benefits of supplemental iron on motor development.

Although the majority of studies have found effects of ID on motor development during infancy, there are only two samples in which long-term motor effects were assessed. Follow-up studies of a Costa Rica sample showed that children who had severe, chronic ID during infancy scored lower on the Bruininks-Oseretsky Test of Motor Proficiency at 5 years and during early adolescence (Lozoff, Jimenez, Hagen, Mollen, & Wolf, 2000; Lozoff, Jimenez, & Wolf, 1991). In a follow-up study in Chile, 5.5-year-old children who had IDA during their first year of life also scored lower on the Bruininks-Oseretsky than children who did not have IDA during infancy (De Andraca et al., 1991). These long-lasting differences, however, do not answer questions about changes in motor development over time. For instance, do children treated for ID in infancy show some evidence of catch up or do they show a widening gap in motor performance? Do their patterns of motor development differ from those of children without ID in infancy? We report here the use of longitudinal analysis (hierarchical linear modeling) to study the effect of ID in infancy on motor development over time.

2. Methods

2.1. Sample

This longitudinal analysis was based on the Costa Rica sample mentioned above. Costa Rica is a Central American country with an excellent record of infant health, but iron supplementation was not routinely recommended at the time the study started. The analysis used the children's iron status measurements and motor development assessments before and after 3 months of iron treatment during infancy, and follow-up motor assessments at 5 years and 11–14 years. All aspects of the research were conducted in collaboration with the Hospital Nacional de Niños, San Jose, Costa Rica, and supported by the US National Institute of Child Health and Human Development.

The first phase of the study involved 191 infants from an urban community near the capital city. Enrollment entailed door-to-door screening of the entire community. 12- to 23-month-old infants who had been born with birth weight ≥ 2.5 kg, of singleton uncomplicated births, and who were free of acute or chronic medical problems were invited to participate. These healthy infants had relatively low lead levels and no evidence of growth failure or other nutrient deficiencies. Iron status in infancy varied from iron sufficiency to moderate iron-deficiency anemia. Details of the original study have been published previously (Lozoff et al., 1987).

In the 5-year follow-up study, 165 children (85% of the original cohort) were evaluated. All but 15 children were assessed within 2 weeks of their fifth birthdays. For the follow-up in early adolescence, 167 (87%) of the original infant cohort participated. The average age at testing was 12.3 years, with a range of 10.9–13.7 years. Included were 22 children who could not be located for the 5-year evaluation and 3 children who were “lost” during the infancy study but located for testing at both follow-ups. Eighteen children who were evaluated at 5 years could not be located. Overall, only 6 of the original infancy sample were completely lost to follow-up.

Parental signed informed consent was obtained by the project pediatrician for all phases of the study. Assent of the child was obtained at the early adolescence follow-up. The infancy and 5-year protocols were approved by the Institutional Review Board of Case Western Reserve University, Cleveland, and subsequent protocols were approved by the Institutional Review Board of the University of Michigan, Ann Arbor. All protocols were approved by ethics

committees of the Hospital Nacional de Niños and the Ministry of Health, Costa Rica, and the Office of Protection from Research Risks, National Institutes of Health.

2.2. Iron status

Iron status in infancy was determined by venous concentrations of hemoglobin (Hb), transferrin saturation, erythrocyte protoporphyrin, and serum ferritin. Iron status varied from iron sufficiency to moderate IDA. Moderate anemia was defined as $Hb \leq 100$ g/L, and nonanemia as $Hb \geq 120$ g/L, with mild anemia and intermediate Hb groups covering the rest of the range in hemoglobin values. ID was defined as a serum ferritin <12 μ g/L and either erythrocyte protoporphyrin ≥ 100 μ g/dL red blood cells or transferrin saturation $<10\%$. Iron sufficiency was defined as normal values on all three measures of iron status. Hematologic response to iron therapy in infancy was excellent with an average Hb increase of 37 g/L among IDA infants. All anemic infants corrected their anemia with 3 months of iron therapy, although most still had biochemical alterations, such as elevated erythrocyte protoporphyrin values. Iron status was excellent during follow-up measurements at 5 and 11–14 years. No child had IDA, and biochemical evidence of ID was present in less than 5%.

At the 5-year follow-up we observed lower mental and motor test scores among the formerly moderate IDA group (Lozoff et al., 1991). These children had chronic, severe ID, since anemia is a late manifestation of ID and Hb levels correspond to severity once anemia occurs. Lower scores were also observed among children who, as infants, had Hb concentrations above the anemia cutoff and ID that did not fully correct after 3 months of iron therapy. They also had evidence of more severe or chronic ID. These groups were therefore combined to form a chronic, severe ID group for comparison with the other children, who had good iron status before and/or after iron therapy in infancy (Lozoff et al., 1991). For simplicity, the chronic, severe ID group will be referred to as ‘chronic ID’ and the rest of the sample as ‘good iron status’. All analyses compare the chronic ID and good iron status groups ($n = 53$ and 132, respectively).

2.3. Assessment of motor development

Motor development during infancy was assessed prior to treatment, after 1 week and after 3 months of treatment. The motor summary score was the Psychomotor Developmental Index (PDI) of the Bayley Scales of Infant Development (Bayley, 1969). The Bayley was used, as it was among the most comprehensive motor measures available in 1981, when the study began. In the Bayley test, which was devised for infants aged 0–30 months, one point is given for each item above baseline that the infant passes, i.e., succeeds in performing. The total number of points that the infant accumulates is transformed, based on the infant's age, into a standardized score. The possible range of standardized scores is 50–150 with mean of 100 and standard deviation of 16.

Motor development at 5 years was assessed using the Bruininks-Oseretsky Test of Motor Proficiency (Bruininks, 1978). Again, this measure was chosen because it was the most comprehensive and most widely used motor test for this age group at that time (1986). The Bruininks-Oseretsky test comprises 46 items, which assess both gross and fine motor functioning of children from 4.5 to 14.5 years old. The items are organized into eight subtests: (1) running speed and agility, (2) balance (static and dynamic), (3) bilateral coordination, (4) strength, (5) upper limb coordination, (6) response speed, (7) visual-motor control, (8) upper limb speed and dexterity. The nature of raw scores on items differs by task (e.g., amount of time to complete the task, the number of units completed within a fixed period of time, the number of errors, etc.). Each raw score is transformed into a point score and summed for the subtest. The total point score for each subtest is then converted into a standard score based on the child's age. The standard scores of all the subtests are summed to create composite sum

standard scores. There are three composite standard scores: (1) Gross motor composite sum (subtests 1–4), (2) Fine motor composite sum (subtests 6–8), and (3) Battery composite sum (all subtests (1–8)). Each composite standard score has a range of 20–80, a mean of 50, and a standard deviation of 10.

In early adolescence, motor development was assessed by the short form of the Bruininks-Oseretsky test (Bruininks, 1978). This test was used for continuity with age 5, but the short form was administered to accommodate other testing demands. Earlier research had shown that the short form could be substituted for the complete battery (Beitel & Mead, 1980). This test includes 14 of the 46 original items. These 14 items are drawn from all eight subtests to create an estimate of general motor proficiency. Based on the participant's age, the sum of the point scores of the 14 items is converted into a standard score with the range of 24–75. In order to use all tests in the same longitudinal analysis, we rescaled the scores of the short and long Bruininks-Oseretsky tests to fit the scale of the Bayley (see below).

The appropriateness of using the standardized scores of the Bruininks-Oseretsky test in other cultures has not been well-studied, although a recent study in an Arab society showed results comparable to the US (Hassan, 2001). The standardized scores also appear to have been appropriate for Costa Rica. The mean scores for the good iron status children at 5 years were at the 50th–51st percentile of US norms, as were the scores for boys in that group at 11–14 years.

2.4. Statistical analysis

2.4.1. Propensity score for background factors—ID often goes along with other individual, family, and/or environmental disadvantages (Grantham-McGregor & Ani, 2001; Lozoff, 1990; Martins, Logan, & Gilbert, 2003; Pollitt, 2000b). Table 1 shows that the chronic ID and good-iron-status groups differed in a variety of ways, some of which could have important influences on motor development. To reduce bias due to these differences, we used propensity score adjustment (D'Agostino, 1998). Propensity scores are increasingly used in epidemiological and medical research to control for multiple background factors in a parsimonious fashion (Rosenbaum, 2002; Rosenbaum & Rubin, 1984). The idea is to create an index of the risk (propensity) for having the condition of interest. The propensity score, consisting of relevant preexisting factors, is then used as a control variable, typically in strata, in analyses of outcome. The propensity score approach is considered a powerful way to strengthen causal inferences in observational studies (Rosenbaum, 2002; Rosenbaum & Rubin, 1984).

In this case, the condition of interest was iron status in infancy (chronic ID v. good iron status). Factors that could influence the probability of being ID in infancy (sex, birth weight, infant feeding practices, age at enrollment, family structure, socioeconomic status, mother's IQ, and quality of the home environment) were included in the propensity score. The propensity score was calculated by predicting iron status membership using multivariate logistic regression. The propensity score for each child was the estimated probability of being in the chronic ID or good iron groups, depending on preexisting differences. Table 1 shows that statistically significant differences between the chronic ID and good iron status groups in preexisting background characteristics were eliminated by propensity score adjustment. Once estimated propensity scores were obtained for each individual, they were stratified into quintiles according to the predicted probability. Propensity score in strata (quintiles) was covaried in subsequent analyses, allowing control for these various preexisting differences in a parsimonious index.

2.4.2. Rescaling motor measures—In order to perform a longitudinal analysis, all motor measures had to have the same scale. Therefore, the short and long Bruininks-Oseretsky test

scores were rescaled to fit the range of the Bayley (50–150). The rescaling was performed using the following equation:

$$X_{\text{rescaled}} = \min_{\text{Bayley}} + \left((\max_{\text{Bayley}} - \min_{\text{Bayley}}) \times \frac{(X_{\text{original}} - \min_{\text{Bruininks}})}{(\max_{\text{Bruininks}} - \min_{\text{Bruininks}})} \right). \quad (1)$$

This process of transforming scores onto a similar scale has been supported in the literature as an appropriate technique for handling test transitions in pediatric longitudinal studies and clinical trials (Coscia, Ris, Succop, & Dietrich, 2003; Lindsey, O'Donnell, & Brouwers, 2000). Following rescaling, the possible range for scores on all tests at all ages was 50–150. The mean and standard deviation of the original and rescaled motor development scores at each assessment are presented in Table 2.

With the rescaled Bruininks-Oseretsky scores, there was a slight decrease in the mean motor score between infancy and 5 years. It cannot be determined whether the explanation for the decrease was due to change in the type of motor assessment used or a real change in motor function. Therefore, we constructed a “test dummy variable” that was incorporated in all subsequent analyses to control for change in motor assessment test. Creating such a dummy variable allowed us to include in one model the data from all the different motor tests, thus enhancing the ability to assess change over time (Lindsey et al., 2000).

2.4.3. Change over time—Longitudinal studies are designed to answer questions concerning individual change over time. In principle, continuous data from longitudinal studies can be analyzed using classical multivariate regression methods. However, these techniques impose model assumptions that were not met in our study. For instance, the age at initial testing varied between 12 and 23 months. In this period of substantial motor development, the average motor ability at 12 months is distinctly different from the average motor ability at 23 months. Thus, one cannot refer to the scores at the time of enrollment as if they were performed at the same age for all infants. Furthermore, because the age at enrollment was different for different participants (Table 2) but all children were tested in a narrow window around their 5-year birthday, the time interval between testing at infancy and testing at 5 years varied. So also did the time interval between testing at 5 years and early adolescence, when children ranged in age from 11 to 14 years. Varying testing times and time intervals between tests violate the basic assumption of classic multivariate regression methods.

To overcome this problem, we conducted longitudinal analysis using SAS Proc Mixed. (This is also known as hierarchical linear modeling analysis.) The approach is based on a mixed effects model in which repeated measures are modeled using a regression model, with parameters that are allowed to vary across and within individuals. Mixed effects models combine two sources of variation: inter-individual and intra-individual. The inter-individual variation was modeled as random effect intercept and random effect slope. The intra-individual variation was modeled as a decreasing function of the time separation between measurements, since points closer together in time are likely to be more correlated than time points further apart. Because the data for each individual is modeled separately in a mixed effects model, it is not assumed that an equal number of repeated observations are taken for each individual or that all individuals are measured at the same points in time. By applying the longitudinal Proc Mixed analysis we were able to use the actual age of testing for each participant, thus employing a uniform time frame for all participants. The advantages of the mixed effects model are that it does not assume an equal number of repeated observations, all available data are used in the analysis, and children for whom some of the observations (but not all) are missing do not need to be excluded.

In the present study, a quadratic model was fit to examine the possibility of nonlinear change processes. The analysis was centered around the first motor assessment, which was performed

at enrollment and before iron treatment. The final mixed model was adjusted for gender, growth, pubertal status, propensity score in quintiles, and a “test dummy variable”. By including gender in the propensity score, we controlled for the possible effect of gender on iron status; by adjusting for gender as a covariate in the longitudinal analysis, we controlled for a possible gender effect on motor scores. Height-for-age z-score (HAZ) was the growth variable most consistently related to motor scores, although significant correlations were still quite low ($.09 < r < .18$). Initial HAZ was substantially correlated with HAZ at all other time points ($.73 < r < .96$). We therefore used it as the growth covariate in the longitudinal analysis. The pubertal status variable was included, since it may affect motor performance in adolescence. As previously reported (Lozoff et al., 2000), pubic hair (measured by Tanner stage) correlated with other measures of pubertal progression in both boys and girls and therefore allowed a measure that could be used with both genders. For comparison with other studies (MacCobb, Greene, Nugent, & O'Mahoney, 2005), we also examined the correlations between PDI and Bruininks-Oseretsky scores.

2.4.4. Patterns of change—We conducted a hierarchical clustering analysis (Blashfield & Aldenderfer, 1978; Everitt, 1980) to determine if children from the iron status groups typically had different motor development trajectories and to explore patterns of change for children within each iron group. The hierarchical clustering analysis used Ward's minimum variance on the Euclidian distances from the standardized motor scores to identify subgroups in our sample, based on the slope of the motor development trajectory. To determine the number of clusters, we used the cubic clustering criterion (CCC). The analysis yielded four main clusters: (1) The ‘stable-low’ cluster, consisting of children who started with a relatively low motor score at enrollment and stayed low over time, (2) the ‘low-increasing’ cluster, consisting of children who started with a relatively low motor score at enrollment but increased their score over time, (3) the ‘stable-high’ cluster, consisting of children who started with relatively high motor score and stayed high over time, and (4) the ‘high-decreasing’ cluster, consisting of children who started with a relatively high motor score and decreased in score over time. We conducted a Chi-square analysis to test for differences in the distribution of children in these four clusters, based on their iron status.

3. Results

There was evidence of a modest degree of stability in relative motor scores from infancy to later ages in this sample. Overall, the correlations between PDI scores and Bruininks-Oseretsky scores at 5 and 11–14 years ranged from .19 to .41 (p values all $< .02$). The longitudinal (hierarchical linear modeling or mixed model) analysis showed significant differences depending on gender and iron status in infancy. The longitudinal trajectories for males differed from females in slope and quadratic term ($F(1, 566) = 5.45, p = .02$), regardless of iron status. Over time males maintained more or less the same motor performance level for age, while females' scores declined towards adolescence. In both iron status groups, males had slightly (but not significantly) higher motor scores than females during infancy and at 5 years. The difference between males and females in both iron groups increased considerably afterwards, statistically significant in early adolescence. At that time point, males of the good iron status group scored 16.1 points higher than the females of that group; males from the chronic ID group scored 16.8 points higher than corresponding females. Children (both males and females) from the good iron status group had, across all ages, significantly higher motor scores than children from the chronic ID group ($F(1, 148) = 13.54, p < .001$). As shown in Fig. 1, there was an initial difference of 9.8 points between the chronic ID and the good iron status groups for both males and females. These differences in the intercept of the trajectories between the two iron groups were statistically significant (p values $< .01$). Analyzing each gender separately, there were no significant differences between the slopes and the quadratic terms of the lines representing the longitudinal motor development of the two iron groups. The absence of

significant differences indicates that the two trajectories were parallel, i.e., the difference in average motor scores between the two iron groups was maintained over time for both males and females (as can also be seen in the figure).

Motor skills are usually divided into gross motor and fine motor skills, but the Bayley test and the Bruininks-Oseretsky short form do not provide separate subscales. However, the 5-year assessment yielded separate gross and fine motor scores. At 5 years it was therefore possible to examine whether gross or fine motor skills contributed more to the observed difference in motor performance between the chronic ID and good iron status groups. Differences were quite similar – 7.5 points in gross motor scores ($F(1, 127) = 5.65, p = .02$) and 5 points in fine motor scores ($F(1, 135) = 4.55, p = .03$).

The relationship between iron status in infancy and the four patterns of change in motor scores that emerged from the hierarchical clustering analysis was statistically significant in Chi-square analysis ($\chi^2(3, N = 185) = 9.02, p = .03$). As can be seen in Fig. 2, chronic ID children were not represented equally in all the clusters. Although they comprised 29% of the overall sample, they accounted for 47% of the ‘stable-low’ cluster. This cluster consisted of children who started with a relatively low motor scores and continued to score low. Conversely, there were disproportionately fewer of them in the ‘stable-high’ cluster – only 15%.

To consider functional significance in another way, we analyzed the proportion of children within each group with scores more than 1 standard deviation (SD) below the mean at each assessment. The proportion with such low scores ranged from 21% to 32% in the chronic ID group, compared to 11–15% in the good iron status group. The differences were statistically significant at every age except 5 years.

4. Discussion

In this study of the effects of ID in infancy on motor development over time, children who had chronic ID in infancy had lower motor scores than children with good iron status, statistically significant at all ages. Mean scores of the chronic ID group were at the lower end of the range considered ‘normal’ (mean ± 1 SD), and more of them had scores more than 1 SD below the US norm at each age. In longitudinal analysis, boys in the chronic ID group continued to have scores at the low end of the normal range at 5 years and in adolescence, showing a parallel but lower motor development trajectory compared to boys with good iron status in infancy. The motor trajectory for the chronic ID girls was also parallel and lower than that of the good iron status girls; girls in general scored much lower than the boys in adolescence. Thus, there was no evidence that children with chronic ID during infancy caught up over time in their motor test scores. Furthermore, chronic ID children were over-represented in a ‘stable-low’ cluster and under represented in the ‘stable-high’ cluster. Both fine and gross motor skills appeared to be equally affected. This finding suggests that ID in infancy contributed to broad early effects on a variety of brain processes and/or structures that are involved in motor production and control.

Recent research points to several central nervous system (CNS) effects of early ID that could help explain our results. Iron is involved in myelin production, and disruption in the availability of iron has been shown to impede myelination (Beard, Wiesinger, & Connor, 2003; Connor & Menzies, 1996; Ortiz et al., 2004). Specifically, ID during gestation and lactation in the rat is associated with changes in myelin components (protein, cholesterol, phospholipids and galactolipids) and compaction at adulthood despite an iron-sufficient diet since weaning (Ortiz et al., 2004).

It is possible that ID during infancy delayed and/or altered the myelination process of the corticospinal tract, which in turn contributed to delay and/or alteration in the normal acquisition

and refinement of motor skills. The corticospinal tract, which encompasses the vast majority of the pyramidal tract fibers, connects motor and sensory regions of the cerebral cortex with the spinal cord and as such, constitutes the main path through which motor commands travel from the brain to the limbs. Myelination of the pyramidal tract is partial at birth and is not completed for several years (Rothwell, 1994). The process of myelination during the initial years of life increases conduction velocity along this tract. Over time, this process enables the refinement of motor performance and improvement in motor skills to adult-like level (Lemon, Olivier, & Edgley, 1997). Indeed, Heinen et al. (1998) have attributed poorer motor performance of children relative to adults to differences in maturation of the corticospinal system, as expressed in differences in central conduction time during application of transcranial magnetic stimulation. More direct support for the idea that ID in infancy has long-lasting effects on myelination in humans comes from a recent study that examined auditory brainstem responses and visual evoked potentials. In 4-year-old children who were treated for IDA during infancy, transmission was slower in both the visual and auditory systems, suggesting that long-lasting effects of early IDA on myelination could be widespread (Algarin, Peirano, Garrido, Pizarro, & Lozoff, 2003).

Another possible explanation for long-term effects of ID on motor function relates to reduced dopamine function, especially in the striatum. In rodent models, reduced brain iron concentration due to severe dietary iron restriction results in changes in the density of D₁ and D₂ dopamine receptors and dopamine transporter in the striatum (part of the basal ganglia) that persist to adulthood despite iron repletion (Beard & Connor, 2003; Lozoff et al., 2006; Youdim, 2000). Even in a more moderate ID rodent model, there are short- and long-term effects on motor behaviors that depend on intact striatal dopamine neurons (Beard et al., 2006; Felt et al., 2006). Long-term potentiation (LTP) and long-term depression (LDP) in the striatum, with the cooperative action of D₁R and D₂R, are thought to play a role in the regulation of motor learning (Nakano, Kayahara, Tsutsumi, & Ushiro, 2000). Thus, persisting changes in striatal D₁R and D₂R densities could alter the process and/or regulation of motor learning in IDA children, despite iron therapy.

Dopaminergic neurotransmission is also important in the motor cortico-basal ganglia-thalamo-cortical loop, which consists of two pathways within the basal ganglia – direct and indirect. The direct pathway, which acts to increase excitatory output from the thalamus to the cortex, contains mainly D₁ dopamine receptors. In contrast, the indirect pathway, which acts to decrease excitatory output from the thalamus to the cortex, contains mainly D₂ dopamine receptors (Obeso, Rodriguez-Oroz, Rodriguez, Arbizu, & Gimenez-Amaya, 2002). Normal motor behavior appears to depend on a balance between the output of the direct and indirect pathways, a balance that both facilitates desired movements and inhibits potentially competing movements. Imbalances between the direct and indirect pathways are hypothesized to lead to hypokinetic syndromes such as Parkinson's disease – with increased output of the indirect pathway relative to the direct pathway – or hyperkinetic syndromes such as Huntington disease with increased output of the direct pathway relative to the indirect one (Nakano et al., 2000). Thus, persisting changes in D₁R and D₂R due to ID in infancy may affect this delicate balance and consequently motor performance.

Dopamine neurons of the substantia nigra also code positive reward expectation errors by increasing their dopamine release to the striatum, to facilitate adaptive changes of synaptic transmission related to reward (Satoh, Nakai, Sato, & Kimura, 2003). Thus, reduced dopamine transporter and receptors in the striatum with early ID may reduce motivation, exploration and learning due to reduced input signaling positive internal reward. A related mechanism through which ID during infancy could have long-term effects is known as 'the functional isolation hypothesis' (Levitsky & Barnes, 1972; Lozoff et al., 1998; Strupp & Levitsky, 1995). According to this hypothesis, reduced activity and exploration and/or changes in affect and attention may

lead ID infants to seek and receive less stimulation from the physical and social environment. Over time these alterations in child and caregiver behavior affect the child's mental, motor, and social-emotional development. Long-lasting alterations in social-emotional and mental development have been observed in the same sample (Lozoff et al., 2000; Lozoff, Jimenez, & Smith, 2006), which could interact with motor development over time to contribute to the long-term effects.

An encompassing framework may incorporate the specific hypotheses mentioned above. This is derived from Johnson's 'neuroconstructivism' or 'interactive specialization' view (Johnson, 2003). According to this framework, brain development is determined by interaction between typical maturation of innate developmental processes and environment. Neurochemical, physiological, and behavioral deviations from 'normal' development may affect the process of brain development and cause the brain to develop somewhat differently. Thus, it is possible that chronic ID during infancy caused some delay or alteration in the infants' motor development while it lasted. The brain of these infants may well have compensated for, and/or adapted to, this deficiency by taking a different course of development. It is possible that, once iron status returned to normal, this adaptation enabled the ID infants to develop motorically at a similar rate as the good iron status infants. However, without an accelerated rate, there was no catch up in motor performance.

Gender issues were not the focus of this study, but the difference in motor performance between boys and girls in adolescence was striking. Poorer motor proficiency in girls, especially in adolescence, has been reported in the past and attributed to both biological and environmental (cultural and social) factors (Thomas & French, 1985). Although biological factors may contribute to this gender difference from a very early age (Piek, Gasson, Barrett, & Case, 2002), their effect is increased substantially during puberty, when boys develop larger muscle mass, larger hearts and consequently larger stroke volume, greater lung capacity, higher pulmonary ventilation and higher oxygen uptake than girls (Bale, Mayhew, Piper, Ball, & Willman, 1992). These structural and physiological changes result in greater increase in speed, strength, power and physical work capacity, resulting in increased gender differences in the performance of many motor tasks, including items on the Bruininks-Oseretsky (Hattie & Edwards, 1987). However, the scores of adolescent girls in Costa Rica were much lower than typically observed. The marked decrease in the girls' motor scores in adolescence in our sample may be due to social and cultural factors that limit girls' motor opportunities, activities, and performance more in Costa Rica than in the US. The extremely low scores of the chronic ID girls should be viewed cautiously, given their small number.

The question of continuity between test scores in infancy and those later on has received little attention with respect to motor proficiency, compared to cognitive functioning. One study addressed this question with the same measures used in our study. That study (with a considerably small sample size than ours) found no correlation between Bayley motor scores in infancy and Bruininks-Oseretsky at 9 years (MacCobb et al., 2005). In contrast, we found continuity with both correlational analyses and the more powerful analytical approach of hierarchical linear modeling. The reason for such differing findings is unknown and warrants further study.

4.1. Limitations

Our relatively small sample consisted of children born healthy at term, who were free of growth faltering or other chronic or acute health problems. Most ID children in the world have more health problems than our sample. Thus, it is not clear to what extent our results generalize to them. More longitudinal research is needed in larger, more varied samples. The limited number of ID girls in our sample limits generalization to females. The use of different tests of motor development in infancy and later ages also presented some challenges in analysis and

interpretation. In addition, the age and duration of onset ID cannot be known with certainty in our study or most previous studies. It is possible that longer duration of ID during early motor development contributed to the observed long-term effects, since our participants were identified at 12–23 months and were therefore likely to have been ID for some time. If their ID started in the 1st year of life, timing may also have played a role, and earlier iron treatment might have reversed or prevented those effects. Furthermore, observational studies such as ours cannot prove that ID caused the effects, even though we controlled for a comprehensive set of background factors. Future research should consider causality and onset age and duration of ID. Such studies would require a different design, such as randomized control trials of preventing ID in infancy.

Longitudinal effects of changes in family and environment were not examined in this study. This question was not our focus and would be better studied in a larger sample with less stability in such important influences as socio-economic status, father absence, etc. Since culture, family, home environment, and socio-economic status (and changes in them) can affect motor development over time, they should be considered in more depth in future research.

4.2. Conclusion

In sum, this study shows that lower motor scores of chronic ID infants did not improve over time despite iron therapy in infancy that corrected IDA. ID children who started with relatively low motor scores were more likely to score lower through early adolescence. There was no evidence of catch-up in motor scores. Thus, iron treatment at the age of 12–23 months did not prevent long-term effects of ID in infancy on motor development. These results emphasize the importance of preventing ID, the most common nutrient deficiency in the world.

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Fig 1. Mean trajectories of good iron status (empty symbols) and chronic ID (filled symbols) groups plotted as a function of age for females (dotted lines) and males (solid lines).

Fig 2.
Percentage of chronic ID children within clusters that reflect different patterns of change in motor scores over time.

Table 1
Background characteristics before and after propensity score adjustment

	Chronic iron deficient	Good iron status	<i>p</i> -value before adjustment	<i>p</i> -value after adjustment
(<i>n</i>)	53	132		
Gender (female)	28%	52%	<.01	0.96
Birth weight (kg)	3.1 (0.3)	3.3 (0.4)	.02	0.71
Age at enrollment (mo)	15.8 (3.0)	17.3 (3.2)	<.01	0.99
Never breast feed	15%	4%	.01	0.88
Duration of breast feeding (mo)	5.1 (4.9)	8.0 (6.2)	<.01	0.91
Age cow milk started (mo)	1.2 (0.8)	1.4 (0.8)	.06	0.92
Cow milk (ml/day)	940 (386)	822 (348)	.04	0.82
Bottles (number/day)	4.3 (1.4)	3.7 (1.5)	.01	0.70
Father absent	36%	20%	.02	0.89
Grandparent(s) present	53%	36%	.03	0.87
Socioeconomic status ^a	27.2 (10.8)	31.0 (12.6)	.05	0.81
Mother's IQ	76.1 (12.8)	84.8 (12.4)	<.001	0.94
HOME score in infancy ^a	26.3 (6.5)	31.1 (6.2)	<.001	0.92

Note. Values are mean (SD) for continuous variables and percent for categorical variables. Due to a skewed distribution, the age of starting cow milk was log-transformed. The area under the receiver operating characteristic curve (or *C*-statistic) for the propensity score model was *C* = 0.86, indicating good discrimination between iron status groups.

^a Higher scores are better.

Table 2

Original mean (SD) and rescaled (bold) raw scores at the different assessments

	Original score (mean $\pm$ SD)			
	Chronic iron deficiency		Good iron status	
	Male (n = 38)	Female (n = 15)	Male (n = 64)	Female (n = 68)
Age (months)	16.1 $\pm$ 3.3	14.9 $\pm$ 1.7	17.2 $\pm$ 3.2	17.5 $\pm$ 3.2
Bayley PDI – pretreatment	105.2 $\pm$ 19.5	104.6 $\pm$ 17.1	114.3 $\pm$ 15.1	111.2 $\pm$ 14.5
Age (months)	16.7 $\pm$ 3.3	15.5 $\pm$ 1.7	17.7 $\pm$ 3.2	18.0 $\pm$ 3.1
Bayley PDI – 1 week	106.5 $\pm$ 17.6	105.7 $\pm$ 16.4	114.8 $\pm$ 18.0	112.6 $\pm$ 15.8
Age (months)	19.6 $\pm$ 3.3	18.3 $\pm$ 1.6	20.5 $\pm$ 3.2	20.9 $\pm$ 3.1
Bayley PDI – 3 months	112.7 $\pm$ 14.5	105.0 $\pm$ 11.6	114.6 $\pm$ 15.7	112.8 $\pm$ 14.4
Age (months)	60.5 $\pm$ 2.2	59.9 $\pm$ 0.3	60.1 $\pm$ 0.3	60.3 $\pm$ 0.6
5-Year Bruininks-Oseretsky	45.2 $\pm$ 9.0	40.9 $\pm$ 10.3	49.9 $\pm$ 10.2	49.8 $\pm$ 9.2
5-Year Bruininks-Oseretsky rescaled	91.9 $\pm$ 15.1	84.8 $\pm$ 17.1	99.8 $\pm$ 17.0	99.6 $\pm$ 15.3
Age (months)	145.1 $\pm$ 7.3	144.7 $\pm$ 7.8	150.8 $\pm$ 7.0	147.6 $\pm$ 8.2
Adolescence Bruininks-Oseretsky short	46.4 $\pm$ 13.2	37.8 $\pm$ 11.3	51.6 $\pm$ 11	43.4 $\pm$ 10.7
Adolescence Bruininks-Oseretsky short rescaled	93.9 $\pm$ 26.0	77.1 $\pm$ 22.1	104.1 $\pm$ 21	88.0 $\pm$ 21.1