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Hemoglobin Status Associate with Performance IQ but not Verbal IQ in Chinese Pre-school Children

Yuexian Ai[1], **Sophie R. Zhao**[2,*], **Guoping Zhou**[1], **Xiaoyang Ma**[2], and **Jianghong Liu**[2,**]
[1]Jintan People's Hospital, Jintan, Changzhou City, China

[2]University of Pennsylvania School of Nursing, Philadelphia, PA, USA

Abstract

Background—Despite the body of literature that links anemia with poorer cognition in children and the evidence that the severity of the effects of anemia on children's cognition vary in different populations, few studies have investigated the effects of anemia on the cognitive development of Chinese children.

Study Design—This longitudinal cohort includes 171 children from a developing region of China. Hemoglobin and iron levels were taken when the children were 4 years old. At age 6, the children's cognition was tested with Chinese WPPSI. Psychosocial information was also used in analyses.

Results—Results showed that the children who had low Hb levels had significantly lower scores in PIQ, but not VIQ. Although blood Fe levels were not shown to moderate the link between hemoglobin levels and IQ, we found children who performed the best on IQ tests exhibited low iron levels concurrent with high hemoglobin levels, whereas the group who performed the worst exhibited high iron but low hemoglobin levels. We also found that psychosocial adversity did not differ significantly between children who had normal or low hemoglobin levels, although the effect of hemoglobin on PIQ became only suggestive after controlling for psychosocial adversity, therefore the relationship is not causal but only a suggestive association.

Conclusion—Our findings are in agreement with literature on the negative effects of anemia on children's cognition and point to the possibility that the portions of the brain associated with PIQ components are particularly affected by low Hb during crucial periods of development.

Keywords

anemia; Chinese children; cognition; hemoglobin; intelligence; iron; performance IQ; verbal IQ

Introduction

Despite the widespread research and intervention efforts in place for the past decades, anemia still remains one of the most prevalent nutritional deficiency disorders in the world today, particularly in pregnant women and young children. According to a recent study[1], children living in developing countries such as Southern Asian and Africa are particularly affected, especially within the age group of 5 years and below. An estimated 30–80% of pre-school children in developing countries were anemic at age 1 year[2]. Anemia is the condition of less than the normal quantity of blood hemoglobin and poses a significant threat to

**Corresponding Author: Jianghong Liu, PhD, Assistant Professor, Schools of Nursing and Medicine University of Pennsylvania, 418 Curie Blvd., Room 426, Claire M. Fagin Hall Philadelphia, Pennsylvania 19104-6096, Tel: (215) 898-8293, jhliu@nursing.upenn.edu.
*Co-first authors

physiological and psychological health. This is due to decreases in oxygen availability to the body, including tissues and major organs, such as the brain. As a result, there are many symptoms associated with anemia, include both physiological ones, such as cerebrovascular infarction (stroke), and psychosocial ones, such as decreased cognitive abilities and adverse behavioral outcomes because of impairments in normal brain functions.

The most studied causes of anemia are iron deficiency anemia (IDA) and sickle cell anemia. IDA is the most common type of anemia in the world[3] and is caused, as its name suggests, by low levels of iron. Iron serves as the catalytic component of the oxygen-binding portion of hemoglobin (Hb), the iron bearing protein in red blood cells. Insufficient levels of iron leads to catalytically non-functional Hb cells, which in turn leads to hypoxia throughout the body. However, the relationship between anemia and child development is not entirely straightforward. Studies have shown that excess Fe deposits in the brain can lead to abnormalities in lipid oxidation in both laboratory rodents[4] and in cultured human brain cells[5], which is accompanied by decreased learning and motor activities and abnormal neurobehavioral functions[4, 6]. Although no single test exists to test for IDA, the CDC has published guidelines for tests to diagnose IDA, including serum ferritin levels ≤15μg/L, serum transferring receptor concentration >8.5 mg/L, mean cell volume <16%, and red cell distribution width >14%, along with low Hb levels (varies across age groups but averages around 12 g/dL for the majority of the population)[7]. Sickle cell anemia, on the other hand, is an autosomal recessive Hb disorder caused by a homozygous condition of the sickle-shaped Hb allele, which distorts the shape of red blood cells and prevents them from properly carrying oxygen. Diagnosis for sickle cell anemia pertains to laboratory measures to identify the presence of sickled red blood cells. Other forms of anemia include, vitamin deficiency anemia, thalassemia, and aplastic anemia, among others.

A wide body of evidence has linked anemia with poorer performance on cognitive and motor measure in infants, children, and adolescents[8, 9], sometimes even after receiving treatments as young children[10, 11]. The effects of anemia are particularly marked during infancy and early childhood since they are periods of significant growth and development of the central nervous system. As exhibited in numerous animal studies, infancy and early childhood are periods during which major development of large portions of the hippocampus and cortical regions, as well as myelin, dendrite, and synapse formation take place throughout the braine[12, 13]. Disrupting these processes can lead to poorer development in spatial learning and memory[14]. Many studies in the past few decades have shown that anemic children suffer from a wide range of cognitive developmental deficits. Lozoff et al.[15] found that at Hb levels < 10 g/dL, a decline in mental development was observed in human infants and motor development concurrently decreased at Hb levels < 10.5 g/dL. Hb levels have also been found to be positively correlated to various aspects of cognitive functions in preschool children[16], adolescents[17], and adults[18].

It is widely known that the extent and severity of the negative effects of anemia on children's cognitive development can vary in different populations[3, 8]. However, to our knowledge, there has only been one other study[19] investigating the association between anemia and the development of Chinese pre-school children. Compared to the controls, children who suffered from IDA at infancy exhibited behavioral anomalies, including less positive effects and more passive behavior at pre-school age. No 4 study to date has investigated the effects of anemia on the *neuro-cognitive* development in Chinese children. In this paper, we explore the relationship between Hb level and cognition in pre-school age children in a developing region of China. We hypothesize that hemoglobin levels are positively associated with cognition in Chinese pre-school children. We also believe our study will contribute to the literature by adding to the existing body of studies on the effects

of anemia on children across the world, especially in affected regions of developing countries.

Methods

Study site and participants

The current study was part of a larger population-based community cohort study of 1,656 Chinese children (55.5% boys, 44.5% girls). Initially recruited in the spring of 2005, the children were from four preschools in the town of Jintan, located in the southeastern coastal region of Mainland China. Detailed sampling and research procedures of this larger cohort study are described elsewhere[20]. Briefly, the China Jintan Child Cohort Study is an on-going prospective longitudinal study with the main aim of assessing early health risk factors for the development of child neurobehavioral outcomes. This location was chosen because, as a rapidly developing small city, Jintan offers a wide range of industrialization and socioeconomic development within a reasonably geographically contained population.

The current sample consists of 171 six year-old Chinese children (55.6% boys and 44.4% girls.). Written informed consent was obtained from the parents. Institutional Review Board approval was obtained from both the University of Pennsylvania and the ethical committee for research at Jintan Hospital in China.

Blood Hb levels and serum Fe status at age 4 years

Hb level: blood specimens were collected successively in the fall of 2004 by trained pediatric nurses using a strict research protocol to avoid contamination. Approximately 0.5 mL of venous blood was collected in lead-free EDTA tubes and tested at Jintan Maternal Child Health Center. Blood Hb concentration was measured using a 7–22 photoelectric colorimeter. Low Hb levels are defined to be ≤12 g/dL[21] for children in this group, who are 4–6 years old at the time of assessment.

Fe level: blood specimens were frozen and then shipped to the Child Development Center, China Nanjing Medical University, for serum iron (Fe) analysis. Specimens remained frozen at −20°C until analysis. Whole blood concentrations of serum Fe were determined by atomic absorption spectrophotometry (BH model 5.100 manufactured by Beijing Bohu Innovative Electronic Technology Corporation), with duplicate readings taken with an integration time of two seconds. The reliability and validity of the analysis and the detailed analytical procedures have been described previously[22].

It should be noted, at this point, that our study does not include the assessment of IDA, which should include at least three indicators of low Fe, e.g. serum ferritin, serum transferring receptor concentration, mean cell volume, or red cell distribution width. Rather, we assessed serum Fe levels to be used as an approximate indicator for overall Fe status. Using measurements established previously with this cohort[23], low Fe levels are defined to be ≤7.5μg/dL.

IQ Assessment at age 6 years

The IQ data were collected in spring of 2007, when the children were 6 years old and in their last year of preschool (equivalent of Western kindergarten). The children were tested with the Chinese version of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)[24], which was standardized in China in 1988[25, 26] and has been shown to have good reliability in Chinese children[25–28]. The WPPSI consists of 10 subtests. Five of these make up a Verbal IQ (Information, Comprehension, Arithmetic, Vocabulary and Similarities) and

another five comprises the Performance IQ (Object Assembly, Geometric Design, Block Design, Mazes and Picture Completion).

The reliability and validity of the analysis and the detailed analytic procedure have been described previously[29–31]. Complete data on both the blood Hb and IQ variables were available on 145 subjects.

Psychosocial Adversity

Socio-demographic information was collected at the same time as the blood samples when the children were at age 4. The data was obtained from a parental questionnaire which included information on the child's gender, age, mother's and father's education, mother's and father's health, birth complications during pregnancy, parental marriage status, mother's and father's occupation, caregiver details, house size or family size, and living condition. For reasons previously discussed[23], we did not include information on family income as a part of psychosocial adversity measurement, but used house and family sizes instead. Parents filled out the socio-demographic questionnaire during their meetings at the pre-schools. Although the questionnaires were self-administered, research assistants were on-site to assist the parents in filling out the forms.

These demographic indicators are grouped together and referred to collectively as "social adversity" in future analyses. A total psychosocial adversity score was created by adding 1 point for each of the 11 variables mentioned above (excluding the child's gender and age). Complete data for this variable was available on 145 of the children at Age 4.

Representativeness of Groups

At age 4 years, 145 children had complete data on all independent and dependent variables. This group was compared with those without complete data (n=46) on key demographics, gender, and psychosocial adversity. We did not observe significant differences in the group with and without complete data for gender ($\chi^2_1 = 1.098$, $p = 0.296$) or psychosocial adversity ($t_{144}=0.860$, $p = 0.932$). Consequently, the subsamples used were representative of the larger sample.

Statistical Analysis

To test for the effects of low Hb on IQ, univariate analysis of variance (ANOVA) was conducted using IBM SPSS 19 (IBM Corporation 2010). Descriptive statistics (mean and standard deviation) on all measured key variables are presented in Table 1, along with results from Chi-squared correlation analyses among the variables.

Hb levels are classified into three groups with cutoffs at the 25^{th} and 75^{th} percentiles. The three-group classification was used instead of the two-group (low-Hb/normal-Hb with cutoff of 12 g/dL[21]) to better understand the link between Hb and IQ, since our sample size was relatively small (171 children overall). ANOVAs aimed to assess which one of the IQ components was particularly related to Hb.

Our preliminary analyses showed that there is no significant difference in psychosocial adversity between children with normal and low Hb levels (see Table 2). However, to ensure clarity of the results, psychosocial adversity was still entered into analyses as a confounding variable. Gender and Fe status were also entered individually into analyses as interactive independent variables to assess moderation effects. Two-tailed tests of significance were used throughout the analyses and significance was defined as $\alpha \leq 0.10$.

Results

Effect of Low Hb

Mean (SD) IQ scores for each of the 3 Hb groups is given in Table 3. Ad-hoc Tukey tests indicate that significant group differences exist for PIQ (p=0.090) among different Hb groups. Furthermore, it can be observed that at the general trend exists that children who have lower Hb levels also had lower IQ scores. When each of the 10 subtests of the WPPSI was examined individually, we found that the mazes subtest to be significantly associated with Hb levels ($F_{2, 144} = 3.455$, $p = 0.034$). ANOVA results (Table 4) indicate that low Hb at age 4 showed a significant main effect on PIQ, but not VIQ.

Effect Moderators

When serum Fe is entered as a moderator variable in the analyses, ANOVA results did not indicate that any significant main effects or interaction effects between Fe and Hb levels at Age 4. Nevertheless, we did find some interesting trends that children who performed the best on all IQ scales concurrently had high Hb and low Fe, whereas the children who performed the worst had low Hb and high Fe levels.

There were no moderator effects for gender when entered alongside Hb grouping into ANOVA analyses in any of the IQ scores at any time.

Confounding Variables

When social adversity was entered as a confounding variable in the analysis, ANOVA results indicated that adversity had a significant effect on VIQ, but not PIQ. However, after controlling for social adversity, the main effect in Hb levels on PIQ became suggestive ($F_{2, 142} = 1.976$, $p = 0.123$) but still close to significance.

Discussion

The first key finding of our study is that low Hb levels are associated with low PIQ, but not VIQ in Chinese pre-school children. Furthermore, we observed the trend in our data that the children with low Hb levels at ages 4 years generally have lower IQ scores. However, it should be noted again that the associative relationship between PIQ and hemoglobin levels became only suggestive after controlling for social adversity and that the relationship is not causal. These findings are concurrent with established trends in the literature, which show cognitive achievement to be positively correlated with Hb levels [16–18, 32–37]. These findings also point to the possibility that the portions of the brain associated with PIQ components, i.e. spatial memory, visual-perceptual abilities, and psychomotor skills, are particularly affected by low Hb during crucial periods of development in early childhood.

Although the association between Hb-levels and PIQ became only suggestive after controlling for social adversity, the results still warrant discussion. The social adversity variable itself is only significantly associated with VIQ, not PIQ (see Table 4), indicating that social adversity confounds VIQ much more strongly than PIQ. This also suggests that the development of verbal cognition is more susceptible to the influence of socio-economic factors. Indeed, it is not hard to postulate why children's verbal development is more dependent on the psychosocial environment since children's primordial acquisition of verbal skills come from their surrounding environment. It is entirely possible that parents who are better educated have a better understanding of how to provide good child care, including ample early verbal communication and stimulating the child with other forms of social bonding. It is also possible that parents who are economically better off have the resources to provide their children with consistent and higher quality care from third-party providers,

e.g. nannies and day cares. Indeed, research as early as 1984 has found that the overall quality of care was a predictive measure of language development in toddlers, wherein verbal interaction with caregivers was an important determinant of language skill[38]. A more recent study of 501 pre-K children in the US found that a majority of children who lived in poverty showed decrements in language but no other domains of cognition[39]. This finding was echoed in another study which found that, controlling for variance due to family factors, both day care quality and the environment, predicted a significant portion of the variance in children's language development but not their cognitive development[40]. In conclusion, our finding that VIQ is particularly influenced by socio-economic factors is not surprising and indeed has been echoed in literature for many years in numerous studies. However, it should be noted that since psychosocial adversity is a third-variable that serves as a common cause of both Hb levels and VIQ in our data, no conclusions about causality can be made in this current paper regarding the relationship between Hb levels and VIQ.

The second key finding in our study is that children who performed best on IQ tests at age 6 exhibited low Fe levels concurrent with high Hb levels at age 4, whereas the group who performed the worst exhibited high Fe but low Hb levels. Similar findings have also been reported in a study of school-age children in Thailand[41]. In another study in Alabama on fetal Fe status and IQ in children at age 5[42], it was reported that children with moderate serum ferritin levels performed better than children with either very low or very high serum ferritin levels. A possible explanation for this may be that excess Fe in the body has been shown to cause adverse effects. As our study directly measures the excess Fe in the body, it is reasonable that in our data, children who have a lot of serum Fe but not enough Hb perform the worst due to the compounded negative effects of high serum Fe and low Hb. Conversely, children who have very little excess Fe and high Hb performed the best due to the compounded positive effects of low serum Fe and high Hb. Though we did not observe a dose-response relationship between Hb levels and cognitive function in children with low Fe levels as previously reported[41], we did observe an overall trend that children who perform the best were those with high Hb and low serum Fe levels.

It is unclear exactly what is the cause of low Hb levels for those children who exhibited it in our study. Indeed, children with low Hb levels did not exhibit statistically lower Fe levels. While not directly investigated in this paper, it is possible that low Hb levels are a manifestation of various malnutrition. In recent years, an increasing body of evidence has indicated a link between malnutrition and cognitive impairments in children[8, 35, 43–45], which has been supported by animal studies investigating the effects of early malnutrition on brain structure and learning abilities[46–50]. In addition to IDA, there exist other forms of anemia associated with nutritional deficiency, namely folate deficiency anemia and vitamin B_{12} deficiency anemia.

Folate deficiency anemia, otherwise known as megaloblastic anemia, occurs when diet does not provide the body with sufficient folic acid to produce healthy, functional erythrocytes. Vitamin B_{12} deficiency anemia can occur for a variety of reasons, including Crohn's disease, bacteria growth in the small intestine, and the body's self-destruction of the stomach's vitamin B_{12} absorbing cells (as in the case of pernicious anemia). However, the roles that folic acid and vitamin B_{12} deficiency play in cognitive development are not straightforward. For example, in a large scale 2007 study,[51] subjects with low vitamin B_{12}, high serum folate was associated with anemia and cognitive impairment. However, at normal vitamin B_{12} levels, high serum folate was associated with protection against cognitive impairment. The examination of the precise cause of anemia in our subjects is beyond the scope of the present paper; such an exploration would make interesting grounds for future studies.

The mechanism by which low Hb levels influence cognitive development is not clearly understood. However, there have been a number of studies which point to neurological pathways by which anemia can adversely affect the development of the central nervous system. Children who were anemic at infancy exhibited decreased myelination in the auditory and visual systems of the brain[52] as well as alterations in neurotransmitter functions, particularly in the dopamine system[53, 54] and the hippocampus[10, 14], which can then be linked to decreased cognitive reasoning abilities. It has also been previously reported that low Hb levels in 2-year old Chinese children were correlated with incidents of IDA at 10 months[19]. This suggests that the adverse developmental outcomes could be in fact the result of infant IDA, to which low Hb levels in early childhood could be only a symptom of. Unfortunately we do not have the data in our study cohort to test this hypothesis.

Limitations

There are several limitations of this study which must be addressed. Firstly, our sample size of available Hb status is relatively small and thus few conclusions regarding the significance in observed trends could be made. Though our results seem to fit the established trend of the correlation between Hb levels and cognition in other literature, our conclusions can only be suggestive at best due to the statistical constraints of the small sample size.

Secondly, despite the fact that the main effect of Hb was significant in PIQ, after controlling for social adversity, the association became only suggestive ($p = 0.123$), though still close to significance. This finding is important because it points to the possibility that children's high IQ is a result of good socio-economic standing of the parents. This immediately brings forth two possibilities for the source of this relationship: 1) parents who are better off socio-economically can afford better child-rearing resources, and 2) the family's socio-economic status is a proxy for the parents' IQ, which in turn predicts the children's IQ through genetics. Unfortunately, we do not currently have cognitive data on the parents of this study. A more in-depth investigation of the association between socio-economic status and children's IQ which looks more specifically at the role parental IQ may play in the relationship can be the premise of an intriguing study in the future.

Thirdly, we used serum Fe as indicators of Fe status. Although an adequate measure, better indicators would have been serum ferritin and/or serum transferring receptor as serum Fe may be more accurate indicators of Fe stores than true Fe status.

Lastly, we did not take inflammation into account, which might have caused a negative bias in measured serum Fe levels. In future studies, we should take care to measure and adjust for bioindicators of infections, such as C-Reactive Protein and alpha 1-acid glycoprotein.

Conclusions

In conclusion, this prospective longitudinal study included s 2 biomarkers (blood Hb and serum Fe levels) at age 4 and 2 indicators of IQ at age 6. Despite the limitation of the small sample size, the main finding of our study provides evidence that Hb levels in early childhood is positively associated with PIQ, but not VIQ, in Chinese children later at pre-school age of 6 years. Hb levels were not found to be significantly different between children of different psychosocial adversity levels, although the effect of Hb on PIQ became only suggestive after controlling for psychosocial adversity. Furthermore, the Hb-IQ relationship was not found to be moderated by gender or serum Fe levels. Our main finding is in agreement with the existing literature on the effects of anemia on children's cognitive development. Our study is also one of the only two studies to date that quantitatively examine the effects of anemia in Chinese children.

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References

1. Mason J, Bailes A, Beda-Andourou M, Copeland N, Curtis T, Deitchler M, et al. Recent trends in malnutrition in developing regions: vitamin A deficiency, anemia, iodine deficiency, and child underweight. Food Nut Bull. 2005; 26:59–108.
2. WHO. A Guide for Programme Managers. Geneva, Switzerland: 2001. Iron Deficiency Anemia: Assessment, Prevention, and Control.
3. WHO. Worldwide prevalence of anaemia 1993–2005. World Health Organization; 2008. p. 48
4. Castelnau PA, Garrett RS, Palinski W, Witztum JL, Campbell IL, Powell HC. Abnormal iron deposition associated with lipid peroxidation in transgenic mice expressing interleukin-6 in the brain. J Neuropathol Exp Neurol. 1998; 572:268–82. [PubMed: 9600219]
5. Andorn AC, Britton RS, Bacon BR. Ascorbate-Stimulated Lipid Peroxidation in Human Brain Is Dependent on Iron but Not on Hydroxyl Radical. J Neurochem. 1996; 67:717–22. [PubMed: 8764600]
6. Sobotka TJ, Whittaker P, Sobotka JM, Brodie RE, Wander DY, Robl M, et al. Neurobehavioral dysfunctions associated with dietary iron overload. Physiology & Behavior. 1996; 59:213–19. [PubMed: 8838597]
7. CDC. Recommendations to prevent and control iron deficiency in the United States. MMWR Morb Mortal Wkly Rep. 1998; 47:1–29. [PubMed: 9450721]
8. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. Journal of Nutrition. 2001; 131:649s–66s. [PubMed: 11160596]
9. Lozoff B, Corapci F, Burden MJ, Kaciroti N, Angulo-Barroso R, Sazawal S, et al. Preschool-aged children with iron deficiency anemia show altered affect and behavior. J Nutr. 2007; 137:683–9. [PubMed: 17311960]
10. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutrition Reviews. 2006; 64:S34–S43. [PubMed: 16770951]
11. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000; 105:E51. [PubMed: 10742372]
12. Jorgenson LA, Wobken, Jane D, Georgieff, Michael K. Perinatal Iron Deficiency Alters Apical Dendritic Growth in Hippocampal CA1 Pyramidal Neurons. Dev Neurosci-Basel. 2003; 25:412–20.
13. Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK. Perinatal iron deficiency alters the neurochemical profile of the developing rat hippocampus. J Nutr. 2003; 133:3215–21. [PubMed: 14519813]
14. Youdim M. Brain iron deficiency and excess; cognitive impairment and neurodegenration with involvement of striatum and hippocampus. Neurotox Res. 2008; 14:45–56. [PubMed: 18790724]
15. Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, et al. Iron deficiency anemia and iron therapy effects on infant developmental test performance. Pediatrics. 1987; 79:981–95. [PubMed: 2438638]
16. Soewondo S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. Am J Clin Nutr. 1989; 50:667–73. discussion 73–4. [PubMed: 2773844]
17. Nelson M. Anaemia in adolescent girls: effects on cognitive function and activity. Proc Nutr Soc. 1996; 55:359–67. [PubMed: 8832806]
18. Khedr E, Hamed SA, Elbeih E, El-Shereef H, Ahmad Y, Ahmed S. Iron states and cognitive abilities in young adults: neuropsychological and neurophysiological assessment. Eur Arch Psy Clin N. 2008; 258:489–96.

19. Chang SY, Wang L, Wang YY, Brouwer ID, Kok FJ, Lozoff B, et al. Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children. Pediatrics. 2011; 127:E927–E33. [PubMed: 21402624]
20. Liu J, McCauley LA, Zhao Y, Zhang H, Pinto-Martin J. Cohort Profile: The China Jintan Child Cohort Study. Int J Epidemiol. 2010; 39:668–74. [PubMed: 19433517]
21. Wintrobe, MM.; Lee, GR.; Boggs, DR. Clinical Hematology. 8. Lea & Febiger; Philadelphia: 1981.
22. Dong S, Zhu Z, Wea Liu. Determination of Ca, Mg, Fe, Mn, Cu, and Zn in lixin pill by atomic absorption spectrophotometry. Guang Pu Xue Yu Guang Pu Fen Xi. 2001; 21:391–2. [PubMed: 12947677]
23. Liu J, Hanlon A, Shi Z, Dickerman B, Compher C. Micronutrients deficiency and associated sociodemographic factors in Chinese children. World Journal of Pediatrics. 2011 In Press.
24. Wechsler, D. Wechsler Preschool and Primary Scale of Intelligence. The Psychological Corporation; San Antonio, TX: 1967.
25. Gong YX, Dai XY. China-Wechsler Younger Children Scale of Intelligence (C-WYCSI). Psychological Science. 1986:2.
26. Gong YX, Dai XY. China-Wechsler Younger Children Scale of Intelligence. Acta Psychologica Sinica. 1988; 20:364–76.
27. Yang LL, Liu ML, Townes BD. Neuropsychological and behavioral status of Chinese children with acyanotic congenital heart disease. Int J Neurosci. 1994; 74:109–15. [PubMed: 7928100]
28. Zhu YM, Lu SY, Tang CH. The employment of the Wechsler Pre-school and Primary Scale of Intelligence in urban Shanghai [in Chinese]. Information on Psychology Science. 1984; 5:22–29.
29. Bracken BA. Limitations of preschool instruments and standards for minimal levels of technical adequacy. J Psychoeduc Assess. 1987; 5:313–26.
30. DeThorne LS, Schaefer BA. A guide to currently-used child nonverbal IQ measures. American Journal of Speech-Language Pathology. 2004; 13:275–90. [PubMed: 15719895]
31. Gyurke, JS.; Marmor, DS.; Melrose, SE. The assessment of preschool children with the Wechsler Preschool and Primary Scale of Intelligence-Revised. In: ABB, editor. The psychoeducational assessment of preschool children. 3. Allyn & Bacon; Needham Heights, MA: 2000. p. 57-75.
32. Petranovic D, Batinac T, Ruzic A, Ruzic T. Iron deficiency anaemia influences cognitive functions. Med Hypotheses. 2008; 70:70–2. [PubMed: 17574345]
33. Stoltzfus, RJ.; Mullany, L.; Black, RE. Iron deficiency anaemia. In: Ezzati, M.; Lopez, AD.; Rodgers, A.; Murray, CJL., editors. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Vol. 1. World Health Organization; Gevena, Switzerland: 2004. p. 163-209.
34. Lozoff B, Jimenez E, Wolf AW. Long-Term Developmental Outcome of Infants with Iron Deficiency. New Engl J Med. 1991; 325:687–94. [PubMed: 1870641]
35. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000; 105:E51. [PubMed: 10742372]
36. Hurtado EK, Claussen AH, Scott KG. Early childhood anemia and mild or moderate mental retardation. American Journal of Clinical Nutrition. 1999; 69:115–19. [PubMed: 9925132]
37. de Andraca, I.; Walter, T.; Castillo, M.; Pino, P.; Rivera, P.; Cobo, C. Iron deficiency anemia and its effects upon psychological development at pre-school age: a logitudinal study. Nestle Foundation; Lausanne, Switzerland: 1990.
38. McCartney K. Effect of quality of day care environment on children's language development. Dev Psychol. 1984; 20:244.
39. Barbarin O, Bryant D, McCandies T, Burchinal M, Early D, Clifford R, et al. Children Enrolled in Public Pre-K: The Relation of Family Life, Neighborhood Quality, and Socioeconomic Resources to Early Competence. Am J Orthopsychiat. 2006; 76:265–76. [PubMed: 16719646]
40. Dunn L, Beach SA, Kontos S. Quality of the literacy environment in day care and children's development. Journal of Research in Childhood Education. 1994; 9:24–34.

41. Sungthong R, Mo-Suwan L, Chongsuvivatwong V. Effects of haemoglobin and serum ferritin on cognitive function in school children. Asia Pacific Journal of Clinical Nutrition. 2002; 11:117–22. [PubMed: 12074177]
42. Tamura T, Goldenberg RL, Hou JR, Johnston KE, Cliver SP, Ramey SL, et al. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. J Pediatr-Us. 2002; 140:165–70.
43. Galler JR, Ramsey FC, Morley DS, Archer E, Salt P. The Long-Term Effects of Early Kwashiorkor Compared with Marasmus .4. Performance on the National High-School Entrance Examination. Pediatr Res. 1990; 28:235–39. [PubMed: 2122403]
44. Bennis-Taleb N, Remacle C, Hoet JJ, Reusens B. A low-protein isocaloric diet during gestation affects brain development and alters permanently cerebral cortex blood vessels in rat offspring. The Journal of nutrition. 1999; 129:1613. [PubMed: 10419999]
45. Liu J, Raine A, Venables PH, Dalais C, Mednick SA. Malnutrition at age 3 years and lower cognitive ability at age 11 years: independence from psychosocial adversity. Arch Pediatr Adolesc Med. 2003; 157:593–600. [PubMed: 12796242]
46. Morgane PJ, Austin-LaFrance R, Bronzino J, Tonkiss J, Diaz-Cintra S, Cintra L, et al. Prenatal malnutrition and development of the brain. Neuroscience & Biobehavioral Reviews. 1993; 17:91–128. [PubMed: 8455820]
47. Morgane PJ, Mokler DJ, Galler JR. Effects of prenatal protein malnutrition on the hippocampal formation. Neuroscience & Biobehavioral Reviews. 2002; 26:471–83. [PubMed: 12204193]
48. Piñero DJ, Jones BC, Beard JL. Variations in dietary iron alter behavior in developing rats. The Journal of nutrition. 2001; 131:311. [PubMed: 11160552]
49. Tonkiss J, Galler JR. Prenatal protein malnutrition and working memory performance in adult rats. Behav Brain Res. 1990; 40:95–107. [PubMed: 2126733]
50. Tonkiss J, Galler J, Morgane PJ, Bronzino JD, AUSTIN-LAFRANCE RJ. Prenatal Protein Malnutrition and Postnatal Brain Functiona. Ann Ny Acad Sci. 1993; 678:215–27. [PubMed: 8494264]
51. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. The American journal of clinical nutrition. 2007; 85:193–200. [PubMed: 17209196]
52. Algarin C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron Deficiency Anemia in Infancy: Long-Lasting Effects on Auditory and Visual System Functioning. Pediatr Res. 2003; 53:217–23.10.1203/01.PDR.0000047657.23156.55 [PubMed: 12538778]
53. Singh M. Role of micronutrients for physical growth and mental development. Indian J Pediatr. 2004; 71:59–62. [PubMed: 14979388]
54. Liu J, Raine A. The effect of childhood malnutrition on externalizing behavior. Curr Opin Pediatr. 2006; 18:565–70. [PubMed: 16969174]

Table 1

Descriptive Statistics and Chi-squared Correlation among Measured Key Variables

Variable[a] (Mean, SD)	X^2					
	Hb Level	**VIQ**	**PIQ**	**Male Gender**	**Serum Fe Level**	**Social Adversity**
Hb Level[b] **(12.68, 0.87)**	1	0.139*	0.080*	0.032	0.101	0.071
VIQ[c] **(103.08, 12.49)**	---	1	0.301*	−0.011	0.004	−0.271*
PIQ[c] **(107.10, 13.78)**	---	---	1	0.081	−0.022	−0.089
Male Gender[d] **(0.43, 0.50)**	---	---	---	1	0.092	0.03
Serum Fe Level[e] **(7.99, 0.80)**	---	---	---	---	1	−0.035
Social Adversity[f] **(3.08, 2.04)**	---	---	---	---	---	1

[a] Includes only the 145 subjects who have complete data for all variables

[b] Measured at Age 4 in g/dL

[c] Measured at Age 6

[d] Male = 1, Female = 0

[e] Measured at Age 4 in μg/dL

[f] Measured at Age 4; Range=0–11; 11 = greatest severity

* Significant at two-tailed α=0.10

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Table 2

Demographic Measures among Children Who Did or Did Not Have Low Hemoglobin[a] at Ages 4

	Low Hemoglobin				Normal Hemoglobin				Analysis			
Age at Hb Measure	**N**	**% of Group**	**Mean**	**SD**	**N**	**% of Group**	**Mean**	**SD**	**X^2**	**t**	**df**	**p**
Age 4	37				108							
Gender									1.180		1	0.277
Male		16.6				40.7						
Female		9.0				33.8						
Psychosocial Adversity Score[b]			2.74	1.60			3.19	2.17		−1.130	136	0.260

[a] Low Hemoglobin defined as ≤ 12.0 g/dL

[b] Measured at Age 4; Range=0–11; 11 = greatest severity

Table 3

Average IQ scores at Age 6 within each Hb group* at Age 4.

Hb Measurement (Age) and Hb group	VIQ (Age 6) Mean (SD)	PIQ (Age 6) Mean (SD)
Age 4 (N=145)		
Hb ≤ 12g/dL (N=37)	**101.19** (14.41)	**102.95** (15.26)
12 < Hb ≤ 13.3 g/dL (N=76)	**103.64** (12.00)	**108.21** (13.02)
Hb > 13.3 g/dL (N=32)	**103.91** (11.39)	**109.25** (13.14)

*Cutoffs for Hb groups are the 25th and 75th percentiles

Table 4

Results of Univariate Analysis of Variance of the Effect of Hemoglobin Levels[a] at Age 4 on IQ at Age 6

	Main Effect			Moderator Effects						Confound		
	Hemoglobin Level			Gender Interaction			Serum Fe[b] Level Interaction			Psychosocial Adversity		
	F	df	p	F	df	p	F	df	p	F	df	p
Age 4 (N=145)												
VIQ	0.568	2, 142	0.568	1.036	2, 139	0.358	1.118	2, 139	0.330	11.360	1, 137	0.001*
PIQ	2.363	2, 142	0.098*	1.274	2, 139	0.283	0.554	2, 139	0.576	1.513	1,137	0.221

[a] Hemoglobin Levels are defined with cut offs of the 25th and 75th percentile of each respective age group

[b] Measured at Age 4

[c] Measured at Age 4; Range=0–11; 11 = greatest severity

* Significant at two-tailed α=0.10