Published in final edited form as:

Arch Pediatr Adolesc Med. 2003 June ; 157(6): 593–600. doi:10.1001/archpedi.157.6.593.

Malnutrition at Age 3 Years and Lower Cognitive Ability at Age 11 Years:

Independence From Psychosocial Adversity

Jianghong Liu, PhD, Adrian Raine, DPhil, Peter H. Venables, PhD, DSc, Cyril Dalais, MA, and Sarnoff A. Mednick, PhD, DMed

School of Nursing, University of California, Los Angeles (Dr Liu); the Department of Psychology (Drs Raine, Venables, and Mednick) and the Social Science Research Institute (Dr Mednick), University of Southern California, Los Angeles; the Department of Psychology, University of York, York, England (Dr Venables); and the Child Health Project, Quatre Bornes, Mauritius (Mr Dalais)

Abstract

Background—Early malnutrition is linked to poor cognition, but long-term effects have not been extensively examined and psychosocial confounds have not always been controlled.

Objective—To test the hypothesis that malnutrition at age 3 years will be associated with poorer cognitive ability at age 11 years independent of psychosocial confounds.

Design—A prospective, longitudinal study of a birth cohort of 1559 children originally assessed at age 3 years for malnutrition (low hemoglobin level, angular stomatitis, kwashiorkor, and sparse, thin hair) and followed up to age 11 years.

Setting and Participants—A community sample of 1559 children (51.4% boys and 48.6% girls) born between September 1, 1969, and August 31, 1970, in 2 towns in the island of Mauritius, with 68.7% Indians and 25.7% Creoles (African origin).

Main Outcome Measures—Verbal and spatial ability measured at ages 3 and 11 years and reading, scholastic ability, and neuropsychologic performance measured at age 11 years.

Results—Malnourished children had poorer cognition at both ages. Deficits were stable across time, applied to all sex and ethnic groups, and remained after controlling for multiple measures of psychosocial adversity. Children with 3 indicators of malnutrition had a 15.3-point deficit in IQ at age 11 years.

Conclusions—Malnutrition at age 3 years is associated with poor cognition at age 11 years independent of psychosocial adversity. Promoting early childhood nutrition could enhance long-term cognitive development and school performance, especially in children with multiple nutritional deficits.

An Increasing body of evidence indicates a link between malnutrition and poor cognitive ability in children. In particular, there is growing evidence that early malnutrition could affect later cognitive function in childhood.^{1–3} Such prospective findings, which tease out temporal ordering of variables, suggest a causal relationship between poor nutrition and poor cognition. Such a model has received support from animals studies^{4–8} showing that early malnutrition affects brain structure and learning ability.

Despite such evidence, there is a question as to whether the nutrition-cognition link is confounded by psychosocial adversity. For example, several studies^{9,10} have found that controlling for psychosocial adversity attenuates or abolishes the malnutrition-IQ link. Nevertheless, some supplementation trials¹¹ that control for the social environment still show beneficial effects of better nutrition on cognitive ability, although only a few studies^{9,12} have simultaneously controlled for multiple indicators of psychosocial adversity. One aim of this study is to assess whether the malnutrition-poor cognition relationship holds after controlling for general levels of psychosocial adversity. The more specific effect of parental education was also individually examined because some previous studies¹³ have found this variable to be particularly important.

A partial limitation of some longitudinal research on nutrition and cognition is that cognition is often measured at only 1 point, usually years after the nutritional assessment, but not at the time of nutritional assessment itself. Such studies leave unanswered the question of whether the cognitive gap between malnourished and well-nourished children is static, decreases, or increases over time. The present study aims to address this issue by using measures of cognitive outcome at the time of nutrition assessment at age 3 years and again 8 years later at age 11 years.

Relatively few studies^{3,14} on cognitive ability have examined applied cognitive ability such as school performance and reading skills in addition to intelligence. If poor nutrition affects the ability to complete an IQ test but does not affect real-world issues such as school performance, then one could question the practical public health significance of nutrition-IQ relationships. The present study aims to address this issue by using measures of school performance and reading ability at age 11 years alongside IQ measures.

Human and animal studies^{1,8,15,16} have found that iron deficiency and protein-calorie malnutrition are associated with decreased cognitive functioning. On the other hand, the effects of several malnutrition indicators on cognitive deficits have not been extensively examined. Indeed, few previous studies assess more than 1 indicator of malnutrition. It is possible that a dose-response relationship exists such that children with multiple indicators of malnutrition have magnified cognitive deficits in later life. This study aims to examine this issue by using data from an existing longitudinal study to assess whether multiple indicators of malnutrition are associated with an increasing degree of cognitive impairment at age 11 years.

METHODS

PARTICIPANTS

Participants were obtained from a birth cohort of 1795 children from the island of Mauritius. All children born between September 1, 1969, and August 31, 1970, in 2 towns (Vacoas and Quatre Bornes) on the island were recruited into the study between September 1, 1972, and August 31, 1973, when aged 3 years. The 2 towns were chosen to be representative of the ethnic distribution of the whole island.¹⁷⁻²⁰ The sample consisted of boys (51.4%) and girls (48.6%). Ethnic distribution was as follows: Indians, 68.7%; Creoles (African origin), 25.7%; and others (Chinese, English, and French), 5.6%. Census data for the island as a whole indicated 66% Indians, 29% Creoles, and 5% others, indicating that the study largely achieved its goal of sampling a population representative in sex and ethnicity. Following previous work on this population,^{17,19} data analyses were restricted to Indians and Creoles owing to the small sample size of the "other" ethnic category. Verbal informed consent was obtained from the mothers of the participants. Early research activities were conducted according to the principles outlined in the Declaration of Helsinki,²¹ which prevailed in 1972 when the research was initiated and did not require informed consent to be written,

whereas research activities in later years were conducted using principles outlined in the Belmont Report.²² Institutional review board approval for retrospective data analyses was obtained from the University of Southern California and from the University of California, Los Angeles.

CHILDHOOD NUTRITION DEFICITS AT AGE 3 YEARS

The following 4 signs of malnutrition were assessed in an examination conducted by pediatricians of 1559 of the children:

1. Angular stomatitis: Cracking of the lips and corners of the mouth is predominantly a sign of riboflavin deficiency (vitamin B₂), but it also reflects niacin and retinol (vitamin A) deficiency.²³ The base rate for angular stomatitis in the sample was 7.0%.
2. Kwashiorkor: This condition, also known as protein malnutrition, is found in tropical regions and is common in children weaned on a high starch–low protein diet.²⁴ Kwashiorkor is also an indicator of zinc and copper deficiency.²⁵ The term means “red hair” in African dialect, after the classic symptom of this condition, which consists of a reddish orange discoloration of the hair. The base rate for red hair in the sample was 6.8%.
3. Sparse, thin hair: This is a sign of protein-energy malnutrition in particular²⁶ and of malnutrition in general.²⁷ Protein starvation leads to the cessation of hair growth, and zinc and iron deficiency can also lead to thin hair. The base rate for this symptom in the sample was 5.8%.
4. Anemia: Anemia was indicated by a low hemoglobin level, which reflects iron deficiency.²⁸ Hemoglobin levels were assessed from a laboratory test of blood samples drawn from the child. Anemia was defined as a hemoglobin level below 8.5 g/dL. This definition of anemia was consistent with the medical practice in Mauritius in the early 1970s. The base rate of anemia in this sample was 17.0%.

Patients were defined as having nutritional deficits if at least 1 of these 4 indicators was present (22.6% of the sample); the control group consisted of individuals with no indicator present and was viewed as relatively better nourished (77.4% of the sample). To assess for a dose-response relationship between the number of indicators of malnutrition and verbal-spatial ability, participants on whom IQ data were available were categorized into 1 of 4 groups: no malnutrition (n=950 at age 3 years and n=837 at age 11 years), 1 indicator of malnutrition (n=180 at age 3 years and n=189 at age 11 years), 2 indicators (n=48 at age 3 years and n=51 at age 11 years), and 3 indicators (n=15 at age 3 years and n=13 at age 11 years). Because only 2 individuals had all 4 nutrition indicators across both ages, both were retained in the 3 indicators category. Children with significant medical problems of any kind (including malnutrition, scabies, and parasitic worm) were referred to appropriate agencies for treatment,²⁹ but neither these clinical diagnoses nor the treatment outcomes were recorded or coded.

INTELLIGENCE AND COGNITIVE ABILITY AT AGES 3 AND 11 YEARS

Age 3 Years—Measures of verbal, spatial, and total cognitive ability were derived from 6 subtests of the Boehm Test of Basic Concepts–Preschool Version,^{19,30} which assesses basic verbal and visuo-spatial concepts that are fundamental for early school achievement. Full details of measurement, factor structure, reliability, and validity are given by Raine et al¹⁹ and Boehm.³⁰ Data were available on 1260 participants.

Age 11 Years—Estimates of verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ were assessed at age 11 years using 7 subtests of the Wechsler Intelligence Scale for Children.³¹ The similarities and digit span subtests formed an estimate of VIQ, and the block design, object assembly, coding, mazes, and picture completion subtests formed an estimate of PIQ. Data were available on 1385 participants for these 3 measures of IQ.

Scholastic Ability—Scholastic ability was based on scores on 4 standardized academic tests (English, French, mathematics, and environmental studies) given to all 11-year-old children throughout the country. Scores on these tests (graded 0–5) were summed to form an overall index of scholastic ability.^{19,20} Data were available on 1415 participants.

Reading Ability—Reading ability was assessed using the Holborn Reading Scale.³² This word recognition test consisted of 33 sentences of increasing difficulty. Total scores (number of sentences correctly read) were standardized into reading quotients.^{19,20} Data were available on 1263 participants.

Neuropsychologic Ability—Neuropsychologic test ability was assessed using the Trail-Making Test.^{33,34} The 2 components of this task (A and B) assess visuomotor tracking, motor speed, and attention, with Trails B also containing a working memory component.³⁵ Time-to-completion scores for each component were corrected for age by residualization of scores (mean=0, SD=1).^{19,20} Data were available for Trails A on 1238 participants and for Trails B on 1156 participants.

PSYCHOSOCIAL ADVERSITY AT AGES 3 AND 11 YEARS

The psychosocial adversity index at age 3 years was based on 9 variables collected by social workers who visited the homes of the children at age 3 years (see Raine et al^{17,19} for full details). The index was created along lines similar to those described by Rutter³⁶ in 1978 and Moffitt³⁷ in 1990. A total adversity score was created by adding 1 point for each of the following 9 variables: father uneducated, mother uneducated, semiskilled or unskilled occupation, single-parent status, separation from parents, large family size, poor health of mother, teenaged mother, and overcrowded home. Complete data for this variable were available on 1795 of the children at age 3 years.

The psychosocial adversity index at age 11 years was based on 14 variables collected by social workers who visited the homes of the children at age 11 years. A total adversity score was created by adding 1 point for each of the following 14 variables: living in rented accommodations, living in a house without electricity or water, child has neither good toys nor good books, no television, living in poor housing, father uneducated, mother uneducated, parent psychiatrically ill, parent physically ill, teenaged mother (19 years or younger when child was born), single-parent status, separation from both parents, 5 or more siblings, and overcrowded home (≥ 5 family members per house room). Complete data were available on 1272 participants.

POTENTIAL BIAS DUE TO INCOMPLETE DATA

At age 3 years, 1193 participants had complete data on all independent and dependent variables. This group was compared with those without complete data (n=602) on key demographic variables that were available on all participants at age 3 years. Groups did not differ regarding sex ($\chi^2_1 = 0.008$; $P = .93$), ethnicity ($\chi^2_1 = 1.189$; $P = .28$), or total psychosocial adversity score ($t = 1.75$; $P = .08$). Consequently, the subsample was representative of the larger sample on these measures at age 3 years.

At age 11 years, 871 participants had complete data on all variables. This group was compared with those without complete data ($n = 924$) on key demographic variables. Groups did not differ regarding sex ($\chi^2_1 = 2.3$; $P = .13$) or total psychosocial adversity score ($t = 0.607$; $P = .54$). There was a small but statistically significant overrepresentation of Indians in those with complete data ($\chi^2_1 = 4.25$; $P = .04$). Consequently, ethnicity was entered into analyses to assess its role as an effect moderator or a confound.

STATISTICAL ANALYSIS

To test for the effects of malnutrition on cognitive ability, multivariate analysis of variance (MANOVA) was conducted using statistical software (SPSS; SPSS Inc, Chicago, Ill) at each age (3 and 11 years). Malnutrition (present vs absent) was the grouping variable, and the dependent variables were verbal and spatial ability for analyses at age 3 years and VIQ, PIQ, reading skill, school performance, Trails A and B (Trail-Making Test) for analyses at age 11 years. When MANOVAs revealed a significant main effect of malnutrition, univariate F tests (ANOVAs) were conducted to assess which of the dependent variables were related to malnutrition.

To test for the effect of psychosocial adversity as a potential confound, analyses were rerun with adversity entered as a covariate. The effect moderators of sex and ethnicity were assessed by entering these measures as factors alongside nutrition status. To ascertain which specific indicator of malnutrition was linked to cognitive ability, each of 4 indicators was analyzed separately as a grouping variable in separate MANOVAs and follow-up univariate ANOVAs. To test for a dose-response relationship between the number of indicators of malnutrition and cognitive ability, the grouping variable of malnutrition took on 4 levels (0, 1, 2, or 3 indicators) for MANOVAs and univariate ANOVAs. Two-tailed tests of significance were used throughout.

RESULTS

For all analyses herein, full-scale cognitive ability (the summation of verbal and spatial indicators) was not entered into MANOVAs to avoid multicollinearity, but to illustrate findings results report 1-way ANOVA comparisons for these indicators at ages 3 and 11 years.

COGNITIVE ABILITY AT AGE 3 YEARS

Effect of Malnutrition—Mean (SD) scores (and results of specific t test comparisons) for cognitive measures at age 3 years for the malnourished and control groups are given in Table 1. Malnourished children had decreased verbal but not spatial ability at age 3 years. A MANOVA conducted on verbal and spatial ability showed a main effect of group (malnourished vs control) ($F_{2,1190} = 9.31$; $P < .001$), indicating overall reduced cognitive ability at age 3 years in the malnourished group. There was a significant main group effect for verbal ability in the same direction ($F_{1,1191} = 18.32$; $P < .001$) but not for spatial ability ($F_{1,1191} = 1.63$; $P = .20$).

Potential Confounds—Malnourished children were more likely to experience psychosocial adversity than were control children at age 3 years ($t_{1553} = 4.18$), and they also had a less-educated mother ($t = 3.34$) and a less-educated father ($t = 3.4$) than controls at age 3 years ($P < .001$ for all). Consequently, it is possible that psychosocial adversity and parents' education level could account for the main effects of malnutrition. This possibility was tested by entering these 2 constructs as covariates in the previously mentioned MANOVA. The main effects remained significant after controlling for father's education level ($F_{2,1189} = 7.62$), mother's education level ($F_{2,1189} = 7.58$), and total psychosocial adversity at age 3

years ($F_{2,1189} = 6.65$) ($P < .001$ for all). In a strict test of the psychosocial confound hypothesis, all 9 adversity indicators were entered simultaneously as covariates, but the effect of malnutrition remained significant ($F_{2,1081} = 4.45$; $P = .01$).

Creoles were more likely to be malnourished (27.0%) than were Indians (20.6%) ($\chi^2_1 = 6.97$; $P = .01$). After entering ethnicity as a covariate in the previously mentioned MANOVA to control for possible confounding effects, the main effect of malnutrition remained significant ($F_{2,1145} = 9.44$; $P < .001$).

Effect Moderators—There was no interaction between malnutrition grouping and either sex ($F_{2,1188} = 0.034$; $P = .97$) or ethnicity ($F_{2,1144} = 1.17$; $P = .31$) on cognitive measures at age 3 years, indicating that these measures did not moderate the effects of malnutrition.

IQ, SCHOOL, AND NEUROPSYCHOLOGIC TEST PERFORMANCE AT AGE 11 YEARS

Effect of Malnutrition—Mean (SD) scores and results of *t* test comparisons for cognitive measures at age 11 years for the malnourished and control groups are given in Table 1. Malnourished children had decreased cognitive ability at age 11 years. A MANOVA conducted on VIQ, PIQ, reading, school ability, and Trails A and B (Trail-Making Test) showed a significant main effect for malnutrition ($F_{6,864} = 3.29$; $P = .003$). Univariate *F* tests showed significant effects of malnutrition on VIQ ($F_{1,869} = 7.7$; $P = .006$), PIQ ($F_{1,869} = 6.4$; $P = .01$), reading ability ($F_{1,869} = 7.69$; $P = .006$), school performance ($F_{1,869} = 14.9$; $P < .001$), trails A ($F_{1,869} = 10.4$; $P < .001$), and trails B ($F_{1,869} = 6.2$; $P = .01$), indicating decreased overall cognitive ability at age 11 years in malnourished children.

Potential Confounds—Malnourished children were more likely to come from adverse psychosocial backgrounds at age 11 years than were control children ($t_{1,025} = 2.87$; $P = .004$). Therefore, it is possible that psychosocial adversity measured at age 11 years could confound the main effects of malnutrition. This possibility was tested by entering the total psychosocial adversity score at age 11 years as a covariate in the previously mentioned MANOVA. The main group effect remained significant after adjusting for this confound ($F_{6,821} = 2.78$; $P = .01$). Furthermore, parents' education levels were also entered into the previously mentioned MANOVA, but main group effect remained significant after controlling for father's education level ($F_{6,861} = 2.33$; $P = .03$) and mother's education level ($F_{6,861} = 2.15$; $P = .046$). In a strict test of the psychosocial confound hypothesis, all 14 psychosocial adversity indicators at age 11 years were entered simultaneously as covariates, but the effect of malnutrition remained significant ($F_{6,789} = 2.13$; $P = .048$), indicating that malnutrition at age 3 years related to cognitive deficits at age 11 years independent of psychosocial adversity. Similarly, when ethnicity was entered as a covariate in the MANOVA, it did not show any confounding effect ($F_{4,898} = 5.77$; $P < .001$).

Effect Moderators—There were no moderator effects for sex ($F_{4,934} = 0.36$; $P = .84$) or ethnicity ($F_{4,897} = 0.849$; $P = .49$) when these constructs were entered into the MANOVA as factors alongside malnutrition grouping.

IQ ACROSS CHILDHOOD FROM AGES 3 TO 11 YEARS

Because the effects of malnutrition described herein at age 3 years ($n=1193$) are based on a different sample from that used at age 11 years ($n=871$), it can be questioned whether the same results would be obtained when using exactly the same sample size across the 2 ages. Furthermore, one goal of the study was to assess whether cognitive deficits remained stable, increased, or decreased over time. This possibility was tested by conducting repeated-measures MANOVAs on each of verbal, spatial, and total cognitive ability, with time (age 3 or 11 years) as the repeated measure. Results showed significant main effects of the

malnutrition grouping on verbal ability ($F_{1,825} = 11.45$; $P < .001$) and total cognitive ability ($F_{1,825} = 8.27$; $P = .004$), indicating reduced performance across both ages in malnourished children (Figure 1). The main effect of malnutrition on spatial ability was not statistically significant ($F_{1,825} = 2.92$; $P = .09$). No other main effects or interactions with time were significant.

DOSE-RESPONSE RELATIONSHIP

To assess for a dose-response relationship between the number of indicators of malnutrition and cognitive ability, MANOVAs (with 4 groups: 0, 1, 2, or 3 malnutrition indicators) were conducted on cognitive measures at ages 3 and 11 years (Figure 2). Results show a significant main effect for number of indicators on cognitive ability at age 3 years ($F_{6,2378} = 4.50$) and at age 11 years ($F_{6,2172} = 6.59$) ($P < .001$ for both). Significant group effects on univariate F tests were observed for verbal ability ($F_{3,1189} = 6.53$; $P < .001$), spatial ability ($F_{3,1189} = 3.31$, $P = .02$), and total cognitive ability ($F_{3,1189} = 6.04$; $P < .001$) at age 3 years and for VIQ ($F_{3,1086} = 8.52$), PIQ ($F_{3,1086} = 10.98$), and full-scale IQ ($F_{3,1086} = 12.14$) ($P < .001$ for all) at age 11 years.

INDIVIDUAL COMPONENTS OF MALNUTRITION

Results of MANOVAs and follow-up univariate ANOVA conducted on each of the 4 malnutrition indicators for cognitive measures at ages 3 and 11 years are given in Table 2. Results showed that low hemoglobin level was most strongly and consistently related to poor cognition at both ages. The MANOVAs indicated that angular stomatitis and kwashiorkor were also significantly related to cognitive indicators at age 11 years, but kwashiorkor was not related to cognition at age 3 years. Finally, sparse, thin hair was related to cognitive indicators at age 3 years but not at age 11 years.

COMMENT

The key findings from this study are that malnutrition at age 3 years is associated with poorer verbal and full-scale cognitive ability at age 3 years and poorer VIQ, spatial IQ, full-scale IQ, reading ability, and school and neuropsychologic performance at age 11 years. Critically, the deficits remained after controlling for up to 14 psychosocial adversity variables at age 11 years. Furthermore, the study showed significant dose-response relationships between the number of indicators of malnutrition and the extent of cognitive deficits at age 11 years, indicating that children who have more indicators of malnutrition are more likely to have lower cognitive ability. In addition, cognitive deficits in the malnourished group remained stable over time and were as strong at age 11 years as at age 3 years. Finally, the effect of malnutrition on later cognitive deficits did not differ between boys and girls or Indians and Creoles, as indicated by a failure of these measures to significantly moderate the group effect of malnutrition. Findings support the view that early childhood malnutrition is a potential risk factor for later cognitive deficits and, from a pediatric perspective, raise the possibility that promoting early childhood nutrition could enhance children's long-term cognitive development and school performance.

Some previous studies^{9,16,38} argue that the malnutrition-IQ link is abolished after controlling for psychosocial and environmental confounds, whereas other studies^{10,39} that control for these confounds have been criticized for not adequately controlling for diverse psychosocial and environmental confounds. To better address this issue, this study took into account 9 different psychosocial deficits at age 3 years and 14 psychosocial deficits at age 11 years in assessing the relationship between nutritional status at age 3 years and cognitive status at age 11 years, as well as testing for the individual effect of parental education. Results remained significant for all analyses. These results suggest that nutritional deficits

cannot easily be explained by psychosocial deficits, and they strengthen the case for nutritional deficits playing a direct role in shaping cognitive functioning. Nevertheless, we caution that other variables that are not controlled for such as prenatal factors (eg, low birth weight) could still play a role in predisposing to poor cognition and malnutrition.^{16,38}

The robustness of the malnutrition–poor cognition link is exemplified with reference to 4 factors: type of cognitive outcome, sex, ethnicity, and repeated time points. Three different forms of cognitive functioning—standardized intelligence and concept formation, neuropsychologic ability, and school performance—were all shown to be poorer in malnourished children. These effects applied to boys and girls and to Indians and Creoles, indicating that malnutrition effects are invariant to sex and ethnicity. Furthermore, this study establishes that cognitive deficits are in place at an early age and 8 years later. The fact that the same results are found for different cognitive measures, time points, and groups suggests, but does not prove, that early malnutrition predisposes to cognitive deficits.

Some previous studies on early malnutrition and later cognition examined only a single nutrition indicator (eg, iron deficits only). Although use of multiple indicators has been strongly advocated,⁴⁰ few studies have implemented this recommendation. In addressing this issue, it was found that the number of malnutrition indicators (0, 1, 2, or 3) present was strongly associated with the degree of cognitive deficit. For example, total IQ at age 11 years decreased by 3.3 points with 1 indicator present, 9.0 points with 2 indicators, and 15.3 points with 3 indicators (Figure 2). This dose-response relationship not only further supports the view that malnutrition pre-disposes to poor cognition but also indicates that children with multiple nutritional deficits are increasingly handicapped and could especially benefit from targeted intervention. However, these new findings require further replication and extension before practical applications are drawn.

Previous studies⁴¹ have been criticized for not assessing indicators of micronutrients in addition to protein-energy malnutrition. In our study, we attempted to address this issue by analyzing 4 individual indicators of malnutrition. Results indicated that low hemoglobin level was most strongly and consistently related to poor cognition at both ages, with the exception of spatial ability at age 3 years (Table 2). The finding that low iron level (as measured by hemoglobin) was the only indicator related to all 3 forms of cognition at both ages is consistent with experimental studies^{15,42} in humans claiming beneficial effects of iron supplements on cognition in children, although several findings have been mixed, for example, those of Pollitt et al.⁴³ Furthermore, experimental animal studies indicate that iron is involved in DNA synthesis, neurotransmitter production and function, brain myelination,⁴⁴ and cerebellar white matter formation.⁴⁵ On the other hand, the strength of the findings for hemoglobin may be because this was the most common indicator of malnutrition and increased statistical power for this analysis. Nevertheless, these findings further support the consideration of iron supplementation in future intervention research on cognitive functioning, although other indicators of malnutrition should not be discounted.

Kwashiorkor was also less strongly, but nevertheless significantly, related to cognition at age 11 years, whereas sparse, thin hair was linked to cognition at age 3 years. These 2 indicators reflect protein and zinc deficiencies,⁴⁶ deficits that have been shown in animal studies^{40,47} to affect enzymes involved in neurotransmission, DNA, RNA, and protein synthesis and essential amino acids during brain development. Furthermore, rats fed a low-protein diet show reduced brain weight and low forebrain DNA concentrations,⁴ whereas diets reduced in zinc produce reductions in whole brain, hippocampus, and cerebral weight.⁴⁸ It is possible, therefore, that low protein and zinc levels are factors that help account for the relationship between malnutrition and poor cognition in humans.

Angular stomatitis, an indicator of predominantly vitamin B₂ deficiency⁴⁹ (but also vitamin A²³) was significantly related to cognition at ages 3 and 11 years, although not as strongly as for hemoglobin level (Table 2). Although clear links have been established between vitamin A and cognition,^{40,42,50} to our knowledge, no previous study has examined the relationship between vitamin B₂ deficiency and childhood cognition. The exact mechanism relating vitamin B₂ (riboflavin) deficiency to cognition is currently unknown. However, it is known that riboflavin enhances the hematologic response to iron,⁵¹ and, consequently, riboflavin deficiency may result in iron deficiency and affect cognition through the same routes as for hemoglobin.

There are several limitations to the study that should be acknowledged. First, because malnutrition was assessed at age 3 years only, we cannot ascertain whether the cause of poor cognitive ability at age 11 years is due to malnutrition only in the first 3 years, when brain development reaches a critical stage, or whether it is produced by sustained malnutrition throughout childhood. Second, the conservative definition of anemia could result in some individuals in the control group having mild levels of malnutrition rather than having good nutrition, a fact that would underestimate the true strength of the relationship obtained between malnutrition and cognition. Third, not all children could be followed up to age 11 years, and slightly more Indians than Creoles were represented, although the results did not show ethnicity to be an effect moderator.

CONCLUSIONS

In conclusion, this prospective longitudinal study conducted on a large sample that included 4 indicators of malnutrition and 3 cognitive measures assessed 8 years apart showed malnutrition at age 3 years to be related to poor cognitive ability at ages 3 and 11 years. These findings applied to boys and girls and to Indians and Creoles. Controlling for up to 14 indicators of psychosocial adversity did not abolish the malnutrition–poor cognition relationship. Children with 3 indicators of malnutrition had a 15.3-point deficit in IQ at age 11 years. Findings suggest that promoting early childhood nutrition could enhance long-term cognitive development and school performance, especially in children with multiple nutritional deficits. The fact that cognitive deficits are not only important in their own right but also contribute to public mental health problems such as schizophrenia, depression, and violence^{52–54} highlights the central importance of a full understanding of the role of malnutrition in relation to poor cognition and mental health status.

Acknowledgments

This research was supported by predoctoral fellowship 1 F31 NR07518-02 from the National Institute for Nursing Research, Bethesda (Dr Liu); Independent Scientist Develop Award K02 MH01114 (Dr Raine) and Research Scientist Award 5 K05MH00619 (Dr Mednick) from the National Institutes of Health, Bethesda; a Scholar-in-Residence Award from the Borchard Foundation, Woodland Hills, Calif (Dr Raine); grants from the Medical Research Council, Leverhulme Trust, and Mental Health Foundation, London (Dr Venables); and a grant from the Ministry of Health of the Mauritian Government, Port Louis, Mauritius.

REFERENCES

1. Galler JR, Ramsey FC, Morley DS, Archer E, Salt P. The long-term effects of early kwashiorkor compared with marasmus, IV: performance on the national high school entrance examination. *Pediatr Res.* 1990; 28:235–239. [PubMed: 2122403]
2. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. *J Nutr.* 2001; 131(suppl 2):649S–666S. [PubMed: 11160596]
3. 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]

4. 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. *J Nutr.* 1999; 129:1613–1619. [PubMed: 10419999]
5. Morgane PJ, Austin-LaFrance R, Bronzino JD, et al. Prenatal malnutrition and development of the brain. *Neurosci Bio behav Rev.* 1993; 17:91–128.
6. Morgane PJ, Mokler DJ, Galler JR. Effects of prenatal protein malnutrition on the hippocampal formation. *Neurosci Bio behav Rev.* 2002; 26:471–483.
7. Pinero D, Jones B, Beard J. Variations in dietary iron alter behavior in developing rats. *J Nutr.* 2001; 131:311–318. [PubMed: 11160552]
8. Tonkiss J, Galler JR, Shukitt-Hale B, Rocco FJ. Prenatal protein malnutrition impairs visual discrimination learning in adult rats. *Psychobiology.* 1991; 19:247–250.
9. Galler JR, Ramsey F, Forde V. A follow-up study of the influence of early malnutrition on subsequent development, IV: intellectual performance during adolescence. *Nutr Behav.* 1986; 3:211–222.
10. Pollitt E. Developmental sequel from early nutritional deficiencies: conclusive and probability judgements. *J Nutr.* 2000; 130(suppl 2):350S–353S. [PubMed: 10721904]
11. Pollitt E, Gorman KS, Engle PL, Martorell R, Rivera J. Early supplementary feeding and cognition: effects over two decades. *Monogr Soc Res Child Dev.* 1993; 58:1–99. [PubMed: 8272081]
12. Pollitt E, Durnin JV, Husaini M, Jahari A. Effects of an energy and micronutrient supplement on growth and development in undernourished children in Indonesia: methods. *Eur J Clin Nutr.* 2000; 54(suppl 2):S16–S20. [PubMed: 10902983]
13. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet.* 1992; 339:261–264. [PubMed: 1346280]
14. Pollitt E. Iron deficiency and educational deficiency. *Nutr Rev.* 1997; 55:133–141. [PubMed: 9197133]
15. Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *Lancet.* 1996; 348:992–996. [PubMed: 8855856]
16. Grantham-McGregor SM, Walker SP, Chang S. Nutritional deficiencies and later behavioural development. *Proc Nutr Soc.* 2000; 59:47–54. [PubMed: 10828173]
17. Raine A, Venables PH, Mednick SA. Low resting heart rate at age 3 years predisposes to aggression at age 11 years: evidence from the Mauritius Child Health Project. *J Am Acad Child Adolesc Psychiatry.* 1997; 36:1457–1464. [PubMed: 9334560]
18. Raine A, Reynolds C, Venables PH, Mednick SA, Farrington DP. Fearlessness, stimulation-seeking, and large body size at age 3 years as early predispositions to childhood aggression at age 11 years. *Arch Gen Psychiatry.* 1998; 55:745–751. [PubMed: 9707386]
19. Raine A, Yaralian P, Reynolds C, Venables P, Mednick S. Spatial but not verbal cognitive deficits at age 3 years in persistently antisocial individuals. *Dev Psychopathol.* 2002; 14:25–44. [PubMed: 11893093]
20. Raine A, Reynolds C, Venables PH, Mednick SA. Stimulation seeking and intelligence: a prospective longitudinal study. *J Pers Soc Psychol.* 2002; 82:663–674. [PubMed: 11999930]
21. World Medical Association. Declaration of Helsinki: Recommendations Guiding Doctors in Clinical Research Adopted by the 18th World Medical Assembly. Helsinki, Finland: World Medical Association; 1964.
22. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research. Washington, DC: US Dept of Health and Human Services; 1979. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.
23. Wong, DL.; Hess, CS. *Clinical Manual of Pediatric Nursing.* St Louis, Mo: Mosby–Year Book Inc; 2000.
24. Manary MJ, Broadhead RL, Yarasheski KE. Whole-body protein kinetics in marasmus and kwashiorkor during acute infection. *Am J Clin Nutr.* 1998; 67:1205–1209. [PubMed: 9625094]

25. Subotzky EF, Heese HD, Sive AA, Dempster WS, Sacks R, Malan H. Plasma zinc, copper, selenium, ferritin and whole blood manganese concentrations in children with kwashiorkor in the acute stage and during refeeding. *Ann Trop Paediatr.* 1992; 12:13–22. [PubMed: 1376581]
26. Friedman M, Orraca-Tetteh R. Hair as an index of protein malnutrition. *Adv Exp Med Biol.* 1978; 105:131–154. [PubMed: 727011]
27. Spencer LV, Callen JP. Hair loss in systemic disease. *Dermatol Clin.* 1987; 5:565–570. [PubMed: 3301113]
28. Gibson, RS. *Principles of Nutritional Assessment.* Oxford, England: Oxford University Press; 1990.
29. Bell, B. Primary Prevention of Schizophrenia in High-Risk Groups: Report on a Working Group, 9–12 June, 1975. Copenhagen, Denmark: World Health Organization; 1977. A longitudinal psychophysiological study of 3-year-old Mauritian children: the Joint Child Health Project; p. 24–26.
30. Boehm, A. *Boehm Test of Basic Concepts—Preschool Version.* San Antonio, Tex: Psychological Corporation; 1986.
31. Wechsler, D. *Wechsler Preschool and Primary Scale of Intelligence.* San Antonio, Tex: Psychological Corporation; 1967.
32. Pumfrey, PD. *Reading Tests and Assessment Techniques.* 2nd ed.. London, England: Hodder & Stoughton; 1985.
33. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills.* 1958; 8:271–276.
34. Reitan RM. Correlations between the Trail-Making Test and the Wechsler-Bellevue Scale. *Percept Mot Skills.* 1959; 9:127–130.
35. Lezak, MD. *Neuropsychological Assessment.* 2nd ed.. New York, NY: Oxford University Press; 1983.
36. Rutter, M. Family, area, and school influences in the genesis of conduct disorder. In: Hersov, LA.; Shaffer, D., editors. *Aggression and Anti-social Behavior in Childhood and Adolescence.* New York, NY: John Wiley & Sons Inc; 1978. p. 95–113.
37. Moffitt TE. Juvenile delinquency and attention deficit disorder: boys' developmental trajectories from age 3 to age 15. *Child Dev.* 1990; 61:893–910. [PubMed: 2364762]
38. Guesry P. The role of nutrition in brain development. *Prev Med.* 1998; 27:189–194. [PubMed: 9578993]
39. Pollitt E. The developmental and probabilistic nature of the functional consequences of iron-deficiency anemia in children. *J Nutr.* 2001; 131(suppl 2):669S–675S. [PubMed: 11160597]
40. Wasantwisut E. Nutrition and development: other micronutrients' effect on growth and cognition. *Southeast Asian J Trop Med Public Health.* 1997; 28(suppl 2):78–82. [PubMed: 9561639]
41. Pollitt E. Functional significance of the covariance between protein energy malnutrition and iron deficiency anemia. *J Nutr.* 1995; 125(suppl):2272S–2277S. [PubMed: 7542708]
42. van Stuijvenberg ME, Kvalsvig JD, Faber M, Kruger M, Kenoyer DG, Benade AJ. Effect of iron-, iodine-, and beta-carotene-fortified biscuits on the micronutrient status of primary school children: a randomized controlled trial. *Am J Clin Nutr.* 1999; 69:497–503. [published correction appears in *Am J Clin Nutr.* 1999;69:1294]. [PubMed: 10075336]
43. Pollitt E, Watkins WE, Husaini MA. Three-month nutritional supplementation in Indonesian infants and toddlers benefits memory function 8 y later. *Am J Clin Nutr.* 1997; 66:1357–1363. [PubMed: 9394687]
44. Shankar N, Tandon OP, Bandhu R, Madan N, Gomber S. Brainstem auditory evoked potential responses in iron-deficient anemic children. *Indian J Physiol Pharmacol.* 2000; 44:297–303. [PubMed: 10941617]
45. De los Monteros AE, Korsak RA, Tran T, Vu D, De Vellis J, Edmond J. Dietary iron and the integrity of the developing rat brain: a study with the artificially reared rat pup. *Cell Mol Biol (Noisy-le-grand).* 2000; 46:501–515. [PubMed: 10872738]
46. Albers SE, Brozena SJ, Fenske NA. A case of kwashiorkor. *Cutis.* 1993; 51:445–446. [PubMed: 8519189]

47. Pfeiffer CC, Braverman ER. Zinc, the brain and behavior. *Biol Psychiatry*. 1982; 17:513–532. [PubMed: 7082716]
48. Keller KA, Chu Y, Grider A, Coffield JA. Supplementation with L-histidine during dietary zinc repletion improves short-term memory in zinc-restricted young adult male rats. *J Nutr*. 2000; 130:1633–1640. [PubMed: 10827222]
49. Beers, MH.; Berkow, R., editors. *Merck Manual of Diagnosis & Therapy*. 17th ed.. Whitehouse Station, NJ: Merck & Co Inc; 1999.
50. Persson V, Ahmed F, Gebre-Medhin M, Greiner T. Relationships between vitamin A, iron status and helminthiasis in Bangladeshi school children. *Public Health Nutr*. 2000; 3:83–89. [PubMed: 10786727]
51. Fishman SM, Christian P, West KP. The role of vitamins in the prevention and control of anaemia. *Public Health Nutr*. 2000; 3:125–150. [PubMed: 10948381]
52. Sheitman BB, Murray MG, Snyder JA, et al. IQ scores of treatment-resistant schizophrenia patients before and after the onset of the illness. *Schizophr Res*. 2000; 46:203–207. [PubMed: 11120432]
53. Austin MP, Mitchell P, Wilhelm K, et al. Cognitive function in depression: a distinct pattern of frontal impairment in melancholia? *Psychol Med*. 1999; 29:73–85. [PubMed: 10077295]
54. Raine, A. *The Psychopathology of Crime: Criminal Behavior as a Clinical Disorder*. San Diego, Calif: Academic Press; 1993.

What This Study Adds

Previous studies have shown that malnutrition is related to poor cognitive ability in children. However, few prospective longitudinal studies controlled for multiple indicators of psychosocial adversity, measured several malnutrition indicators, assessed multiple cognitive measures across time, and assessed for a dose-response relationship between malnutrition and IQ.

Results show that children with malnutrition at age 3 years have lower verbal and spatial cognitive ability at ages 3 and 11 years. These deficits were stable across time, applied to boys and girls and to all ethnic groups, and remained after controlling for 14 measures of psychosocial adversity. A dose-response relationship was observed between malnutrition and cognition, with children with several indicators of malnutrition having a 15.3-point deficit in IQ at age 11 years. Findings suggest that better attention to nutrition could have significant implications for cognitive development in children and adolescents.

Figure 1. Verbal (A), performance (B), and full-scale (C) cognitive ability at ages 3 and 11 years in the malnourished and control groups.

Figure 2.
Dose-response relationship between number of malnutrition indicators present and verbal, spatial, and full-scale cognitive ability at age 3 years (A) and age 11 years (B).

Cognitive Measures and Results of t Test Comparisons at Ages 3 and 11 Years in the Malnourished and Control Groups*

Table 1

Measure	Malnourished Group	Control Group	t Test	df	P Value
Age 3 y					
Verbal IQ	96.93 (14.36) (n = 243)	100.92 (15.04) (n = 953)	4.30	1194	.001
Spatial IQ	98.95 (13.52) (n = 260)	100.34 (15.21) (n = 993)	1.34	1251	.18
Full-scale IQ	96.93 (14.36) (n = 243)	100.92 (15.04) (n = 950)	3.73	1191	.001
Age 11 y					
Verbal IQ	96.16 (15.40) (n = 253)	100.90 (14.41) (n = 837)	4.51	1088	.001
Spatial IQ	96.23 (15.41) (n = 253)	100.75 (14.55) (n = 837)	4.28	1088	.001
Full-scale IQ	95.83 (15.49) (n = 253)	100.88 (14.43) (n = 837)	4.80	1088	.001
Reading	76.81 (56.58) (n = 253)	95.11 (55.30) (n = 840)	4.59	1091	.001
School performance	7.63 (6.48) (n = 268)	10.33 (7.07) (n = 924)	5.64	1230	.001
Trail's A	0.24 (1.10) (n = 245)	-0.049 (0.95) (n = 827)	4.04	1070	.001
Trail's B	0.20 (1.07) (n = 215)	-0.023 (0.98) (n = 783)	2.89	996	.004

* Data are given as mean (SD) scores.

Table 2
Components of Malnutrition in Relation to Cognitive Measures at Ages 3 and 11 Years

Measure*	Anemia			Angular Stomatitis			Kwashiorkor			Sparse, Thin Hair		
	F Test	df	P Value	F Test	df	P Value	F Test	df	P Value	F Test	df	P Value
Age 3 y												
Overall MANOVA	5.43	2,1206	.005	8.45	2,1341	.001	0.79	2,1341	.045	7.00	2,1341	.001
Verbal IQ	10.82	1,1207	.001	11.94	1,1342	.001	1.24	1,1342	.26	14.00	1,1342	.001
Spatial IQ	1.34	1,1207	.25	16.39	1,1134	.001	0.94	1,1342	.33	2.35	1,1342	.13
Full-scale IQ	8.69	1,1207	.003	16.39	1,1342	.001	1.57	1,1342	.21	11.85	1,1342	.001
Age 11 y												
Overall MANOVA	6.43	6,878	.001	2.14	6,968	.047	2.14	6,969	.047	1.45	6,969	.19
Verbal IQ	17.89	1,883	.001	3.55	1,973	.06	3.32	1,974	.07	0.87	1,974	.35
Spatial IQ	27.82	1,883	.001	0.90	1,973	.34	1.97	1,974	.16	0.49	1,974	.48
Full-scale IQ	31.48	1,883	.001	1.98	1,973	.16	3.02	1,974	.08	0.04	1,974	.84
Reading	13.91	1,883	.001	2.20	1,973	.14	4.84	1,974	.03	1.79	1,974	.18
School performance	29.40	1,833	.001	6.48	1,973	.01	6.38	1,974	.01	1.69	1,974	.20
Trails A	3.91	1,883	.048	6.94	1,973	.009	9.08	1,974	.003	0.81	1,974	.37
Trails B	7.43	1,883	.007	3.71	1,973	.05	2.80	1,974	.09	2.80	1,974	.09

Abbreviation: MANOVA, multivariate analysis of variance.

* Trails A and B are from the Trail-Making Test.