

## EARLY CHILDHOOD DIARRHEA IS ASSOCIATED WITH DIMINISHED COGNITIVE FUNCTION 4 TO 7 YEARS LATER IN CHILDREN IN A NORTHEAST BRAZILIAN SHANTYTOWN

MARK D. NIEHAUS, SEAN R. MOORE, PETER D. PATRICK, LORI L. DERR, BREYETTE LORNTZ, ALDO A. LIMA,  
AND RICHARD L. GUERRANT

*Brown University, Providence, Rhode Island; Johns Hopkins University School of Medicine, Baltimore, Maryland; Department of Pediatric Psychology, Kluge Children's Rehabilitation Center, University of Virginia, Charlottesville, Virginia; KCRC Pediatric Psychology, University of Virginia, Charlottesville, Virginia; Division of Geographic and International Medicine; University of Virginia School of Medicine, Charlottesville, Virginia; Unidade de Pesquisas Clínicas HUWC/CCS, Universidade Federal do Ceará, Porangabussu, Fortaleza, CE, Brazil; Division of Geographic and International Medicine and Office of International Health, University of Virginia School of Medicine, Charlottesville, Virginia*

**Abstract.** Diarrhea is well recognized as a leading cause of childhood mortality and morbidity in developing countries; however, possible long-term cognitive deficits from heavy diarrhea burdens in early childhood remain poorly defined. To assess the potential long-term impact of early childhood diarrhea (in the first 2 years of life) on cognitive function in later childhood, we studied the cognitive function of a cohort of children in an urban Brazilian shantytown with a high incidence of early childhood diarrhea. Forty-six children (age range, 6–10 years) with complete diarrhea surveillance during their first 2 years of life were given a battery of five cognitive tests. Test of Non-Verbal Intelligence-III (TONI) scores were inversely correlated with early childhood diarrhea ( $P = .01$ ), even when controlling for maternal education, duration of breast-feeding, and early childhood helminthiasis (*Ascaris* or *Trichuris*). Furthermore, Wechsler Intelligence Scale for Children (WISC-III) Coding Tasks and WISC-III Digit Span (reverse and total) scores were also significantly lower in the 17 children with a history of early childhood persistent diarrhea (PD;  $P < .05$ ), even when controlling for helminths and maternal education. No correlations were seen between diarrhea rates and Wide Range Assessment of Memory and Learning subtests or WISC-III Mazes. This report (with larger numbers of participants and new tests) confirms and substantially extends previous pilot studies, showing that long-term cognitive deficits are associated with early childhood diarrhea. These findings have important implications for the importance of interventions that may reduce early childhood diarrheal illnesses or their consequences.

### INTRODUCTION

Diarrhea in developing countries is a leading cause of child morbidity and mortality and a serious cause and effect of malnutrition. Numerous studies have assessed the effects of early childhood malnutrition (including micronutrient deficiency, anemia, and helminthiasis) on cognitive development,<sup>1</sup> but no other studies to our knowledge have specifically addressed the possible long-term impact of early childhood diarrhea (ECD; the number of episodes of diarrhea in the first 2 years of life) on cognitive function in later childhood. Such an effect, as has been shown for intestinal helminth infections for example, would have tremendous importance in helping to demonstrate the potential lasting impact of these common early childhood illnesses and this an even greater urgency for their control.

Since August 1989, we have conducted intensive surveillance for diarrheal diseases and nutritional status among a cohort of children born into an urban Brazilian shantytown.<sup>2</sup> Building on our studies showing long-term associations of ECD with reduced physical fitness<sup>3</sup> and growth,<sup>4,4a</sup> we undertook the current analysis to determine whether ECD burdens associated with reduced cognitive function were found among this cohort's oldest children. Our purpose was to examine whether ECD correlates with reduced cognitive function 4 to 7 years later as assessed by the Test of Nonverbal Intelligence (TONI-III) and other testing and whether early childhood persistent diarrhea (defined as a diarrheal illness lasting 14 days or more) correlates with reduced performances on WISC-III coding tasks and reverse and total digit span and other tasks.

### METHODS

All 47 cohort children (27 girls, 20 boys; age range, 6–10 years; mean, 8 years, 2 months  $\pm$  10 months SD), who had complete diarrhea surveillance data from their first 2 years of life and who had reached 6 years of age (appropriate for testing) were invited to participate after parental informed consent was obtained. Maternal education was assessed both dichotomously (completion of primary school; i.e., 8th grade or not) as well as continuously (actual number of years of mothers' schooling; available for 39 of the children). An episode of diarrhea is defined as three or more liquid stools per day separated from other illnesses by at least 2 diarrhea-free days; an episode of persistent diarrhea was defined as an episode lasting 14 days or more. One child declined to participate. The other 46 completed the battery of five cognitive tests, including the Test of Non-Verbal Intelligence (3rd edition; TONI-III); Wide Range Assessment of Memory and Learning (WRAML) subtests: Visual Learning and Delayed Recall; Wechsler Intelligence Scale for Children (3rd edition; WISC-III) Coding; WISC-III Mazes; and WISC-III Digit Span (forward and reverse). Peter D. Patrick, a pediatric neuropsychologist, and Lori L. Derr, a cognitive therapy psychologist selected the tests and trained Mark D. Niehaus (who was unaware of diarrhea histories) as tester to administer the tests in a standardized manner with instructions in Portuguese. Tests used were standardized psychometric matrix learning tests and an organized memory test, selected for their relative language and culture independence. The TONI-III has been validated in three groups who do not have English as their first language, including comparison studies with

TABLE 1

Demographic characteristics, early childhood diarrhea burdens, and anthropometry for 46 children, ages 6–10 years old, in Fortaleza, Brazil (N = 46)

Cohort characteristics	No.	Mean ± SD
Mean age (years, months)	–	8 ± 10
Sex		
Male	19 (41%)	
Female	27 (59%)	
Mean no. early-childhood diarrhea at 0–2 years	46	10.2 ± 7.6
Birth weight (g)	46	3275 ± 415
Nutritional status at time of study		
Mean height-for-age Z	38	0.16 ± 0.9
Mean weight-for-age Z	38	–0.18 ± 1.4
Mean weight-for-height Z	36	–0.56 ± 1.3
Maternal education		
Below primary school	39 (85%)	
Primary school or above	7 (15%)	
Monthly income*		
Below 1 minimum salary	22 (48%)	
1 minimum salary or above	24 (52%)	

\* 1 minimum wage = US\$102/month.

more than 1,700 Hispanic children who do not have English proficiency as well.<sup>5</sup> In addition, three cohort children, not eligible for this study because of incomplete surveillance data, were selected for pilot testing to confirm that the tests were usable in this setting. Test scores were validated by the child psychologist and converted into scaled, age-appropriate scores wherever possible.

All tests were administered in Portuguese with the aid of a Brazilian health care worker dedicated to this project. The testing location was in a quiet, isolated environment. Total testing time averaged 50 minutes. Each child was tested in two sessions with a 30-minute break in between. The test givers were unaware of children's illness histories until testing was completed for all children.

## RESULTS

The characteristics of the study population are shown in Table 1. The mean number of episodes of diarrhea in their first 2 years of life was 10.2 (± 7.6 SD); only 15% of mothers had completed primary schooling; nearly half had household incomes less than \$102 per month. Anthropometry measures are shown.

As shown in Figure 1, TONI-III quotients were associated with the number of episodes of early childhood diarrhea (ECD), even after controlling for maternal education, measured as completion or noncompletion of primary school (8th grade); and for helminthiasis (22 of the 46 children had *Ascaris lumbricoides* or *Trichuris trichiura*) during the first 2 years of life ( $P = .049$  by regression analysis). Only 2 of 18 children tested in the last 12 months before cognitive testing had intestinal helminths. ECD was also significantly associated with reduced TONI-III quotients independent of hematocrits, which were available for 39 of these children. Finally, not surprisingly, a higher level of maternal education (completion of primary school) was positively correlated with the child's cognitive function, as measured by the TONI-III ( $P = .001$ ), even though controlling for this (along with hel-

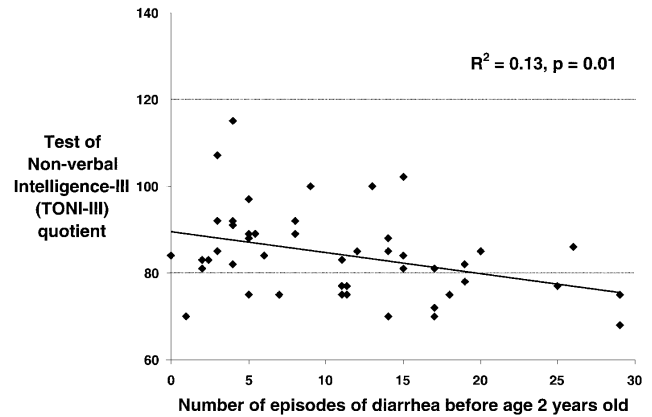


FIGURE 1. Correlation of Test of Non-Verbal Intelligence scores at 6 to 10 years of age with number of diarrhea episodes in the first 2 years of life in 46 Gonçalves Dias children.

minths) or for duration of breast-feeding did not remove the correlation of reduced TONI-III scores with early childhood diarrhea. Further refinements of maternal education by actual years of maternal education (available for 39 of these children) also showed a correlation with children's TONI scores ( $P = .002$ ); controlling for actual years of maternal education still left a strong trend of negative correlation of diarrhea episodes with TONI scores ( $P = .075$ ).

Table 2 shows the regression analyses of TONI-III scores with early childhood diarrhea, controlling for nutritional status as well as for socioeconomic status and intestinal parasitic infections. Although HAZ was correlated with TONI-III scores ( $P = .01$ ), when HAZ and ECD were included in the same model, ECD was slightly more significant than HAZ as a predictor of TONI (for ECD  $P = .09$  and for HAZ  $P = .110$ ). Neither ECD nor HAZ was a significant ( $P < .05$ ) predictor of TONI, independent of the other variable (i.e., ECD was just as good, if not better, a predictor of TONI results as present nutritional status).

Finally, as shown in Figure 2, WISC-III coding task, total digit span, and reverse digit span scores were each signifi-

TABLE 2

Regression analyses of Test of Nonverbal Intelligence-III (TONI-III) scores versus early childhood diarrhea (0–2 years old) in 46 children, (age range, 6–10 years), controlling for nutritional status, socioeconomic status, and intestinal parasites at 0 to 2 years.

	TONI-III score	
	R <sup>2</sup>	P*
Anthropometric covariate		
None	.135	.012
Height for age Z	.267	.129†
Weight for age Z	.301	.091†
Weight for height Z	.236	.046†
Birth weight	.141	.020
Socioeconomic covariate		
Maternal education (±1 primary school)	.315	.053
Monthly income (< or ≥ 1 salary)	.154	.017
Intestinal parasites at 0–2 years		
<i>Cryptosporidium</i> *	.168	.005
<i>Giardia</i> †	.168	.038
Helminths‡	.138	.016

\* p is for negative correlation between TONI-III scores and early childhood diarrhea.

† For HAZ n = 42; for WAZ n = 38, and for WHZ n = 36.

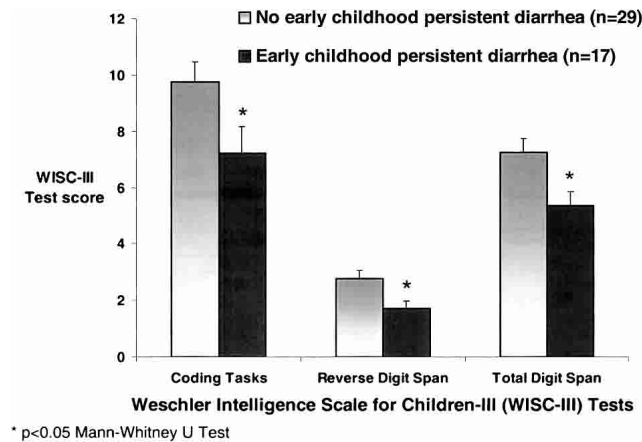


FIGURE 2. Reduced Weschler Intelligence Scale for Children (WISC-III) testing scores in Coding and Digit Span (reverse and total) in 6- to 10-year-old children with one or more persistent diarrheal illnesses in their first 2 years of life ( $n = 17$ ) compared with neighborhood controls who did not have a diarrheal illness lasting 14 days or more in their first 2 years of life ( $n = 29$ ).

cantly lower in the 17 children who experienced persistent diarrheal illnesses in their first 2 years of life, again controlling for maternal education and helminthiasis by Mann-Whitney U test. WRAML Visual Learning and Delayed Recall and WISC-III mazes and Digit Span (forward) results were not correlated with early childhood diarrhea.

## DISCUSSION

Key to an accurate assessment of the global burden of diarrheal diseases (as by disability adjusted life years, or DALYs) is a full appreciation of their long-term impact. Our findings that ECD is correlated with reduced cognitive function 4 to 7 years later as measured by TONI-III and WISC-III Digit Span (forward and total) and Coding and after controlling for maternal education and helminthiasis. In addition, our findings provide new evidence that heavy diarrhea burdens early in life may have important lasting consequences. These findings, now in 46 children with a new test (TONI-III), substantially extend our initial report of long-term associations of ECD with reduced fitness and cognitive function.<sup>3</sup>

Although severe malnutrition, intestinal helminthiasis, and iron deficiency have been associated with cognitive impairment in school-aged children,<sup>1,6</sup> we now report associations of early childhood diarrheal episodes and persistent diarrhea with long-term reductions in cognitive function as assessed by the relative language- and culture-independent TONI-III. Furthermore, these associations of early childhood diarrhea with reduced cognitive function are independent of intestinal helminthic infections and of anemia. The magnitude of reduction seen with the average diarrhea burden of 10.2 episodes of diarrhea in the first 2 years of these children's lives is 5.6%. The reductions in WISC-III scores with persistent diarrheal illnesses ranged from 25% to 65%. Furthermore, in our initial report, cognitive function reductions correlated with ECD independent of growth shortfalls, which were also significantly associated with ECD.<sup>3</sup> TONI testing, like WISC-III Coding and Digit Span, provides a sensitive generalized measure of overall cortical intellectual capability and concentra-

tion; WRAML and WISCIII mazes, which were not affected, more selectively evaluate memory and prospective reasoning.

Although diarrhea, especially persistent diarrhea, is correlated with reduced nutritional status, both early childhood diarrhea and nutritional status are independently correlated with impaired cognitive function. Although this correlation of diarrhea in the first 2 years of life with later reductions in cognitive function cannot attribute causality, the huge importance of early childhood years in human brain development has been repeatedly emphasized.<sup>7-9</sup> Thus, the additive and lasting effects of early childhood diarrhea and malnutrition are of potential paramount importance in the development to full functional capacity. When taken with impaired fitness (that correlates in adults with impaired work productivity)<sup>10</sup> and with impaired growth, the additional impact of early childhood diarrhea on cognitive function even further magnifies its potential lasting "disability costs." Furthermore, these findings likely represent a "best case" scenario in that our long-term follow-up (with its concomitant education about breast-feeding, oral rehydration, and treatment of recognized helminthic infections) has been associated with reduced diarrhea rates and improvement in nutritional status over the study period,<sup>11</sup> effects that we have not seen in nearby shantytown communities not under study (Lima and Guerrant, unpublished observations). Finally, treatment of helminth infections has been shown to improve cognitive function in Indonesian children aged 6 to 8 years<sup>12</sup> and Jamaican children aged 6 to 10.<sup>12,13</sup> If confirmed in other areas, these findings will greatly expand our understanding of the DALY impact of early childhood diarrhea and thus the value of interventions that reduce these illnesses or their impact.

Future studies should focus on early childhood diarrhea and specific cognitive skills, including attention, concentration, working memory, psychomotor persistence and nonverbal reasoning, assessing cognitive function at intervals after early childhood diarrhea, and establishing whether a threshold effect exists. Furthermore, despite the relative homogeneity of this shantytown population, subtle differences in maternal education may well (and likely do) influence both diarrhea and cognitive development. We have controlled for known factors such as recent helminths and anemia. Other illness were not sufficiently prevalent to analyze separately; no major other illness were identified in these children. Clearly, more extensive studies are warranted to determine the possible mechanisms and implications of these findings as well as to assess the cost-effectiveness of interventions to avert this potentially huge disability impact.

Reprint requests: Richard L. Guerrant, Division of Geographic and International Medicine, University of Virginia, P.O. Box 801379, Charlottesville, VA 22908-1379, Telephone: 434-924-9671, Fax: 434-977-5323, E-mail: guerrant@virginia.edu.

Addendum: After these studies were done, reported at NIH (May 2000) and submitted for publication, Berkman et al. reported that among children in Peru, severe stunting and possibly *G. lamblia* infection in the first two years of life are associated with poor cognitive function at nine years of age (Berkman DS et al Lancet 359: 564-571, 2002).

## REFERENCES

1. Grantham-McGregor S, 1995. A review of studies of the effect of severe malnutrition on mental development. *J Nutrition* 125(Suppl): 2238S.

2. Lima AM, Moore SR, Barboza MS, et al., 2000. Persistent diarrhea signals a critical period of increased diarrhea burdens and nutritional shortfalls: a prospective cohort study among children in northeastern Brazil. *J Infect Dis* 181: 1643–1651.
3. Guerrant DI, Moore SR, Lima AAM, et al., 1999. Association of early childhood diarrhea and cryptosporidiosis with impaired physical fitness and cognitive function four-seven years later in a poor urban community in Northeast Brazil. *Am J Trop Med Hyg* 61: 707–713.
4. Moore SR, Lima AAM, Schorling JB, Conaway M, Guerrant RL, 1999. Early childhood diarrhea & helminthiases associate with long-term stunting. *Am J Trop Med Hyg* 61: 385.
- 4a. Moore SR, Lima AAM, Conaway MR, Schorling JB, Soares AM, Guerrant RL, 2001. Early childhood diarrhoea and helminthiases associate with long-term linear growth faltering. *Int J Epidemiol* 30: 1457–1464.
5. Manual for Test of Nonverbal Intelligence (3rd ed.), 1990. Austin TX: Pro-Ed.
6. Nokes C, Grantham-McGregor SM, Sawyer AW, et al., 1992. Moderate to heavy infections of *Trichuris trichiura* affect cognitive function in Jamaican school children. *Parasitol* 104: 539–547.
7. Dobbing J, 1990. Boyd Orr memorial lecture. Early nutrition and later achievement. *Proc Nutr Soc* 49: 103–118.
8. Dobbing J, Sands J, 1985. Cell size and cell number in tissue growth and development: an old hypothesis reconsidered. *Arch Franc Pediatr* 42: 199–203.
9. Dobbing J, 1985. Infant nutrition and later achievement. *Am J Clin Nutr* 41: 477–484.
10. Ndamba J, Makaza N, Munjoma M, et al., 1993. The physical fitness and work performance of agricultural workers infected with *Schistosoma mansoni* in Zimbabwe. *Ann Trop Med Parasitol* 87: 553–561.
11. Moore SR, Lima AAM, Schorling JB, et al., 2000. Changes over time in the epidemiology of diarrhea and malnutrition among children in an urban Brazilian shantytown, 1989 to 1996. *Int J Infect Dis* 4: 179–186.
12. Hadidjaja P, Bonang E, Suyardi MA, et al., 1998. The effect of intervention methods on nutritional status and cognitive function of primary school children infected with *Ascaris lumbricoides*. *Am J Trop Med Hyg* 59: 791–795.
13. Simeon DT, Grantham-McGregor SM, Callender JE, et al., 1995. Treatment of *Trichuris trichiura* infections improves growth, spelling scores and school attendance in some children. *J Nutr* 125: 1875–1883.