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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

DAVID I. GUERRANT, SEAN R. MOORE, ALDO A. M. LIMA, PETER D. PATRICK, JOHN B. SCHORLING, AND RICHARD L. GUERRANT

Department of Health and Sports Science, University of Richmond, Richmond, Virginia; Division of Geographic and International Medicine, Department of Medicine, Department of Pediatrics, and Division of General Medicine, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia; School of Medicine, Department of Physiology and Pharmacology, Clinical Research Unit, Federal University of Ceará, Fortaleza, Brazil

Abstract. To determine potential, long-term deficits associated with early childhood diarrhea and parasitic infections, we studied the physical fitness (by the Harvard Step Test) and cognitive function (by standardized tests noted below) of 26 children who had complete surveillance for diarrhea in their first 2 years of life and who had continued surveillance until 6–9 years of age in a poor urban community (favela) in Fortaleza in northeast Brazil. Early childhood diarrhea at 0–2 years of age correlated with reduced fitness by the Harvard Step Test at 6–9 years of age ($P = 0.03$) even after controlling for anthropometric and muscle area effects, anemia, intestinal helminths, *Giardia* infections, respiratory illnesses, and socioeconomic variables. Early childhood cryptosporidial infections (6 with diarrhea and 3 without diarrhea) were also associated with reduced fitness at 6–9 year of age, even when controlling for current nutritional status. Early diarrhea did not correlate with activity scores ($P = 0.697$), and early diarrhea remained significantly correlated with fitness scores ($P = 0.035$) after controlling for activity scores. Early diarrhea burdens also correlated in pilot studies with impaired cognitive function using a McCarthy Draw-A-Design ($P = 0.01$; $P = 0.017$ when controlling for early helminth infections), Wechsler Intelligence Scale for Children coding tasks ($P = 0.031$), and backward digit span tests ($P = 0.045$). These findings document for the first time a potentially substantial impact of early childhood diarrhea and cryptosporidial infections on subsequent functional status. If confirmed, these findings have major implications for calculations of global disability adjusted life years and for the importance and potential cost effectiveness of targeted interventions for early childhood diarrhea.

Diarrhea persists as a major health threat for children in developing areas. It remains a leading cause of mortality worldwide, causing more than 3 million deaths each year.[1] However, the true long-term impact among those who live through repeated or prolonged diarrheal illnesses is poorly defined and likely under-recognized.[2] Children in impoverished urban areas of northeast Brazil have rates of diarrheal illnesses that are among the highest in the world in their first 2 years of life,[3] with enterotoxigenic and enteropathogenic *Escherichia coli*, rotaviruses, and Norwalk-like viruses predominating in acute diarrhea[3,4] (Lima AAM and others, unpublished data), and *Cryptosporidium*, enteroaggregative *E. coli*, and toroviruses predominating in persistent diarrhea.[5–8] The global economic disparity is also typified in the state of Ceará where nearly half of the families earn less than $113 per month, many families having at least five members.[9] Favelas are extremely poor urban communities where sewage is visible, mud-brick houses often have only 1–2 rooms, and most have no running water and have pit or no toilets. In this setting, we explored the relationships of early childhood diarrhea with subsequent physical fitness, physical activity, and, in pilot studies, cognitive function.

Few, if any, studies have been conducted to examine the relationship of early childhood diarrheal illnesses to long-term physical fitness and activity or cognitive function. Adams and others conducted a randomized controlled trial of albendazole treatment of children in Kenya with *T. trichiura* (whipworm), *Ascaris lumbricoides* (roundworm), and *A. duodenale* (hookworm) infections.[10] Children who were treated with albendazole had reduced numbers of intestinal worms and experienced better growth rates, increased activity, and an increased appetite compared with the placebo group when tested 9 weeks after treatment.[10]

A subsequent study by this group on the same group of Kenyan school children[11] followed the children for a longer period (4 months) and concentrated on overall physical fitness. The investigators concluded that treatment for hookworm infections increased physical growth (both height and muscular growth), improved heart rate recovery (the Harvard Step Test), and increased the appetites of the children.[11] Furthermore, Nokes and others[12] found that Jamaican children between 9 and 12 years old who had moderate-to-heavy *Trichuris* infections and were randomized to receive 3 daily 400 mg doses of albendazole experienced significant improvements in tests of auditory short-term memory and retrieval of long-term memory when retested with a battery of 8 tests to measure psychological and cognitive function 9 weeks later.[12,13] Analyses such as these of physical fitness, nutritional status and cognitive function have enabled Chan and Bundy to recalculate the long-term impact of childhood helminthic infections on disability adjusted life years to essentially double their previous values.[14,15]

There is no information, however, regarding the long-term effects of common early childhood diarrheal illnesses on physical fitness. We postulated that heavy early childhood diarrheal illness burdens (that we have shown with repeated or persisting illnesses impair growth over a 3–12-month period[16–19]) would have a lasting impact on physical and cognitive functioning into later childhood. Building on methods used in the Kenyan and Jamaican studies of intestinal helminths, and on our long-standing prospective surveillance of children followed from birth, we conducted a study of the associations of early childhood diarrhea and prevalent enteric parasite infections with later physical fitness, physical activity, and cognitive function.

MATERIALS AND METHODS

Population. The study site was Gonçalves Dias (population approximately 1,800), a shantytown in Fortaleza (population approximately 2.3 million), Brazil. Fortaleza is the capital city of the northeast State of Ceará (population approximately 6 million). Prior to the initiation of a collaborative prospective surveillance project between the University of Virginia and the Federal University of Ceará, 24% of children had died in their first 5 years of life, mostly from diarrheal diseases.[20] In 1989, the infant mortality rate in Fortaleza was 56.3/1,000/year (State Secretary of Health). From August 1989 through December 1998, an indigenous field team consisting of 2 study nurses and 2 trained community health workers identified all pregnancies in the community, offered the mothers enrollment, and obtained informed consent for inclusion of the child in the study. After granting informed consent for the study, mothers answered a detailed socioeconomic and demographic questionnaire with assistance from a member of the field team. The study protocol was approved by the Human Investigation Committees of the University of Virginia and the Federal University of Ceará. An episode of diarrhea was defined as $\geq$ 3 liquid stools per 24 hr lasting $\geq$ 1 day, separated from other episodes by 2 or more diarrhea-free days. Analyses of selected pathogens in this and nearby populations have already been completed for *Cryptosporidium*,[18,21,22] enteroaggregative *E. coli*,[23] torovirus,[8] Norwalk virus[4] infections, and on overall illness rates and risk factors for persistent diarrhea (Lima AAM, unpublished data). The current study was conducted as a part of the ongoing, prospective surveillance of a cohort of children followed from birth. All participating children in this study were enrolled at birth and some have been followed at least 6 years and some up to 9 years by prospective twice or three times a week surveillance. Of the total birth cohort of 161 children under current surveillance, there were 28 children between 6.5 and 9 years of age (i.e., appropriate for fitness and cognitive testing by standardized methods used) who had a complete history of diarrheal illnesses on record for their first 2 years of life. As reported elsewhere, overall diarrheal illness rates of 5.25 episodes per child per year, with 8% lasting $\geq$ 14 days, with *Cryptosporidium* found in 4.0%, 8.4%, and 16.5% of the controls, patients with acute diarrhea, and patients with persistent diarrhea, respectively, in this population,[22] with cryptosporidiosis as well as persistent diarrhea associated with increased subsequent diarrheal burdens[18] (Lima AAM and others, unpublished data).

The 28 children were shown how the study procedures were done and offered the option to participate or not. Two of the 28 children chose not to complete 1 of the 2 tests and were excluded from further analyses. All of the remaining 26 children thus met the three following criteria: 1) a complete history of diarrheal illnesses in their first 2 years of life (defined as $>$700 child-days of observation recorded; i.e., $>$ 96% of a possible 730 days), 2) a present age appropriate for study participation, and 3) a willingness to complete all tests administered. We determined *a priori* to use illness histories from the first 2 years of life for 2 reasons: 1) the availability of complete data on a sufficient number of children to initially test our hypothesis that early childhood diarrhea is associated with functional deficits years later, and 2) in our study community (like others worldwide), the highest rates of diarrhea occur among children in their developmentally vulnerable first 2 years of life. These 26 children were from 25 households (one sibling pair was included). We were assisted with the protocol by 1 nurse and 2 health care workers, all Brazilians and former residents of the children's community, and responsible for collecting the triweekly diarrheal histories of the children. Immediately preceding the step test, the weight and height of each child were measured with a single, standard, step scale to the nearest kilogram and measuring tape to the nearest centimeter. We then used these values to calculate height-for-age, weight-for-age, and weight-for-height Z scores for each child using the EPINUT program in EpiInfo (Centers for Disease Control and Prevention, Atlanta GA). In addition, mid-arm circumference and triceps skin-fold thickness were measured using a Lange caliper (Creative Health Products, Plymouth, MI) for calculations of muscle and fat area as described by Harrison and others.[24]

Studies of physical fitness and activity. Heart rate recovery was determined by the Harvard Step Test.[11] Briefly, each child stepped up and down a 22-cm step for 5 min at an average rate of 30 steps/min while wearing a backpack containing 20% of their body mass. The weight in the backpack consisted of 2-kg sandbags. The number of bags used was determined by the mass of the child (rounded to the nearest 10 kg). Immediately following the 5-min step test, radial pulses of the children were taken at 1, 2, and 3 min after exercise. A fitness score was then calculated as follows: (300 sec $\times$ 100) divided by (sum of heart rates at 1, 2, and 3 min following exercise).[25] In this equation, 300 sec represents the duration of the test (5 min) and 100 is used to produce an easily divisible number. Using this equation, fitness scores calculated approximated 100; the higher the score, the better the fitness of the child. This physical fitness index, determined by the Harvard Step Test, provides one of the best recognized indices of fitness in many different settings and cultures.[11,26]

Spontaneous physical activity was measured using motion detectors (Model 101; Kaulins and Willis, Middlebury, CT) as described by Adams and others[10] and Eaton and others.[27] Having undergone extensive evaluation, these motion detectors are watches with springs replaced by a hair spring motion recorder so that movement of the watch prompts the watch hands to move.[10,27] Therefore, activity is measured by the amount of time that has passed while the detector is on a wrist of a subject. To determine a physical activity index, the children participated in 15-min structured play sessions.[9] The sessions consisted of a balloon game. Groups of 3 children each were instructed to keep a normal party balloon in the air for the entire 15 min, trying not to let it touch the ground. The detectors were attached to the dominant hand of each child, which was determined by asking them to write their name on a sheet of paper. After a preliminary test run of the game, it was determined that 3 children at a time in a room or finite space (approximately 20 $\times$ 20 feet) was the optimal setting. In addition, males and females were included in separate groups. Throughout the study, children were given refreshments after the step tests and balloons after the structured play activity.

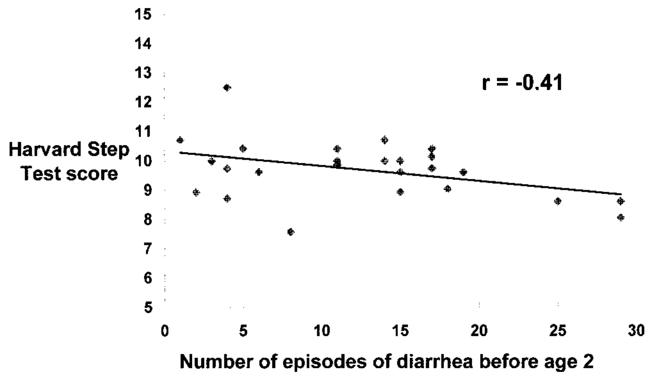

FIGURE 1. Association of episodes of diarrhea in the first 2 years of life with the physical fitness index (the Harvard Step Test) at 6–9 years of age in the cohort (n = 26).

Studies of cognitive development. In addition to determining the impact of diarrheal diseases and enteric infections on anthropometric status and physical function, we conducted a pilot study of their cognitive function. Building on the work on intestinal helminthic infections and cognitive function that have shown impressive results with treatment,[12,13,28–31] we conducted a battery of tests designed to assess information processing and coding skills (using the Wechsler Intelligence Scale for Children–Third Edition, [WISC-III]; The Psychological Corp., San Antonio, TX, 1991 coding tasks), auditory short-term memory (using the WISC-III digit span), dynamic testing of problem solving (using Wechsler Preschool and Primary Scale of Intelligence-Revised [WPPSI-R] mazes; Par, Inc., Odessa, FL), and visual-motor coordination (using McCarthy Scales of Children's Abilities; The Psychological Corp., Test 12, Draw-A-Design, and Draw-A-Child). These tests were selected and evaluated by a child psychologist (PDP) and were administered by 2 of the investigators (DIG and RLG).

To control for additional possible confounders, we assessed the input of hematocrit (available for 24 of these children within 6 weeks of the fitness and cognitive studies), socioeconomic conditions (determined at the time of birth and reassessed at the time of fitness and cognitive studies), and fecal parasites (from specimens collected from 23 of these children within 1 month of the fitness and cognitive testing) on the association between early childhood diarrhea and the outcome measures. In addition, results of parasite examinations on 198 fecal specimens available from these children in their first 2 years of life were also examined ($\geq$ 3 for each child).

All statistical analyses were performed using SPSS (SPSS, Inc., Chicago, IL). Pearson coefficients were calculated for the correlations between diarrhea and Harvard Step Test scores. Partial correlation coefficients were used to adjust for covariates individually.

RESULTS

Twenty-six children (12 boys and 14 girls) completed both the Harvard Step Test and structured play. The mean performance score on the Harvard Step Test was 97.1 (SD = 9.9) and scores ranged from 75.8 to 125.0. Harvard Step Test scores were highly correlated with days of diarrhea (r = −0.42, B = −0.08, 95% confidence interval [CI] = −0.15, −0.01; r^2 = 0.1789, P = 0.031) and with episodes of diarrhea in the first 2 years of life (r = −0.41, B = −0.51, 95% CI = −0.99, −0.03, r^2 = 0.1685, P = 0.034; Figure 1). The impact of early childhood diarrhea was apparent even after controlling for current nutritional status measured as height-for-age, weight-for-age, and weight-for-height Z scores or as arm circumference, muscle area, or fat area, or for anemia (Table 1). Conversely, height-for-age Z scores, weight-for-age Z scores, and weight-for-height Z scores were not significantly correlated with fitness, nor did early childhood diarrhea correlate with current height-for-age Z scores, weight-for-age Z scores, weight-for-height Z scores, arm circumference, muscle area, or fat area.

The 16 *Ascaris* and *Trichuris* infections in 13 of the 26 children (9 had *Ascaris*, 7 had *Trichuris*, 3 had both; found in 198 stool specimens examined from these children in their first 2 years of life) were associated with a significant decrease in the height-for-age Z score at 6–9 years of age (P = 0.002; P = 0.004 when controlling for diarrhea), but still failed to alter the association of diarrhea with fitness (Table 1). Thus, we show that the well-recognized association of intestinal helminth infections with transient growth impair-

TABLE 1

Pearson and partial correlation coefficients between number of diarrheal episodes in first 2 years of life and Harvard Step Test scores (Physical Fitness Index) 4–7 years later, adjusting for anthropometry and anemia at time of study, and intestinal parasites at 0–2 years of age

Variable adjusted for	Correlation between number of diarrheal episodes at 0–2 yo and Harvard Step Test scores		
	R	Partial R	*P*
None (n = 26)	−0.411		0.034
Anthropometric variables (n = 26)			
Height-for-age Z		−0.361	0.076*
Weight-for-age Z		−0.417	0.038
Weight-for-height Z		−0.411	0.041
Anemia (hematocrit) (n = 24)		−0.615	0.004
Intestinal parasites at 0–2 years of age (n = 26)			
Cryptosporidium		−0.199	0.341†
Giardia		−0.477	0.016
Helminths		−0.414	0.040

* Height-for-age Z at time of study was significantly correlated with episodes of diarrhea 0–2 years of age (P = 0.036), but not fitness (P = 0.286).
† *Cryptosporidium* infections (seen in 9 of these 26 children) in the first 2 years of life were correlated with a 2-fold increase in episodes of diarrhea at 0–2 years of age (P = 0.017, by 2-sample *t*-test). Fitness scores in children with early childhood *Cryptosporidium* were 10% lower than in controls (9.0 vs. 10.0; P = 0.008, by 2-sample *t*-test). Adjusting for *Cryptosporidium* removed both the significance of the correlation between diarrhea and fitness and between *Cryptosporidium* and fitness.

TABLE 2

Correlations of early childhood diarrhea with cognitive dysfunction among 26 children (6–9 years old) in an urban Brazilian shantytown

Cognitive test*	Correlation with days of diarrhea 0–2 years old	
	R (n)	*P*
McCarthy Scales Draw-A-Design	−0.49 (26)	0.012†
Backward WISC-III Digit Span	−0.64 (10)	0.049
WISC-III Scaled Coding Test	−0.68 (10)	0.031
Forward WISC-III Digit Span	−0.17 (26)	0.419
WPPSI-R Mazes 5–11	0.05 (26)	0.802

* WISC = Wechsler Intelligence Scale for Children; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence-Revised.

† Correlation remained significant when controlling for hematocrit and early childhood intestinal parasites (*Cryptosporidium*, helminths). Neither intestinal parasites nor hematocrit correlated with cognitive dysfunction.

ment is still seen even 4–6 years later in childhood. Nonnematode helminths and non-pathogenic protozoa seen included *Endolimax nana* (n = 1), *Entamoeba coli* (n = 7), *Hymenolepis nana* (n = 2), and *Cheilomastix mesnili* (n = 2); no *Strongyloides,* hookworm, *Entamoeba histolytica, Balantidium coli,* or *Dientameba fragilis* were seen in specimens examined from these children in their first 2 years of life. When we reviewed all studies of fecal specimens within 1 month of fitness testing, only one of 23 concurrent (< 1 month) stool tests had intestinal helminths (*Ascaris),* thus also excluding present helminth infection as an explanation for the associations we observed. Both *Cryptosporidium* and *Giardia* infections in the first 2 years of life were significantly associated with diarrhea, and early *Cryptosporidium* covaried with diarrhea in associating with impaired fitness 4–7 years later. The correlations of diarrhea with later fitness impairment remained significant when controlling for *Giardia* infection ($P = 0.008$, Table 1). Shigellosis in 5 of these children was not associated with significant reductions in fitness, and correlations of diarrhea with fitness remained significant when controlling for shigellosis ($P = 0.02$). We also reviewed all other illnesses and symptoms in these children in their first 2 years of life (mostly upper respiratory symptoms and dermatologic conditions often present in more than 30% of child-days of observation), as well as pneumonia diagnosed clinically in 12 of these children. Neither correlated with fitness scores, and the association of diarrhea with fitness held when controlling for these other illnesses.

In contrast, there was no correlation of early childhood diarrhea with the activity scores (mean score = 511, SD = 163; range = 245–600; $P = 0.999$) or activity scores with step test scores. In addition, early childhood diarrhea remained significantly correlated with fitness ($P = 0.035$) after controlling for activity scores.

A summary of our pilot testing of cognitive function in these children is shown in Table 2. There were significant negative correlations of McCarthy Draw-A-Design, WISC-III backward digit span, and WISC-III coding tasks with early childhood diarrhea. The correlation of early diarrhea with later cognitive impairment (by McCarthy Draw-A-Design testing) remained significant when controlling for intestinal helminths ($P = 0.017$), hematocrit ($P = 0.031$), and early *Cryptosporidium* infection ($P = 0.005$) (Table 2).

Finally, even though all families lived in the same area in similar conditions, we examined additional potential factors including whether slight differences in water, sanitation, maternal schooling, or monthly income were confounding variables for these observations. At the time of birth, only 12 of these 25 households had piped water, and only 1 had a flush toilet (19 had pit toilets, 4 had none, and 1 used a neighbor's flush toilet). Only 2 of 25 mothers had completed primary education (eighth grade equivalent), and 14 of these 25 households lived on less than $160 per month income. By the time of the present study (1998), 5 more houses had piped water; 7 had new flush toilets, and 2 had pit toilets; 1 mother obtained further schooling and 6 households had increases (while 3 had decreases) in monthly income. None of these socioeconomic indicators or child gender explained our findings of early diarrhea being associated with reduced physical fitness or cognitive function, i.e., fitness scores remained significantly associated with diarrhea independent of water supply, sanitary facilities, child gender, maternal education, or household income by multiple regression analyses.

DISCUSSION

Despite the substantial, known mortality and acute morbidity from diarrheal illnesses, there has been little information on the long-term functional impact of early childhood illnesses on subsequent child development and physical and cognitive function. Based on pioneering studies of the impact of intestinal helminthic infections on physical fitness,[11] physical activity,[10] and cognitive function,[12] we have conducted studies among children followed in our long-term prospective surveillance to examine potential effects of early childhood diarrhea on physical fitness and activity several years later. Because of known short-to-intermediate term impact (over a 3–24-month period) of diarrheal illnesses and enteric infections on nutritional status as well as the reverse,[16,17,32,33] we postulated that there might be a long-term effect of early childhood diarrhea on later nutritional status, and possibly on activity levels or cognitive function. Somewhat to our surprise, we instead found a significant correlation between days of diarrhea in the first 2 years of life and subsequent physical fitness, as measured by the Harvard Step Test, 4.5–7 years later (i.e., 6.5–9 years of age) and in pilot tests, with cognitive function. Children with lower fitness scores were more likely to have experienced more days and more episodes of diarrhea and more cryptosporidial infections during early childhood.

Several other potential confounders must be considered. The correlation between early childhood diarrhea and physical fitness was independent of potential confounders such as sex or any effects due to height-for-age and weight-for-age, weight-for-height, or muscle or fat area. Activity levels, also a potential confounder of the association between early childhood diarrhea and present physical fitness, were not associated with past diarrhea burdens or fitness scores. Other possible confounders, recent or remote intestinal helminth or *Giardia* infections, anemia or socioeconomic status (as determined by mean monthly income, maternal education, or type water supply or toilet facilities) were not associated with fitness, and the fitness association with early childhood diarrhea remained independent of helminthic or *Giardia* infections, anemia, or socioeconomic status in these children.

Regarding possible mechanisms of these long-term effects on physical fitness, we have also examined the calculated muscle and fat areas[24] from arm circumference and skin-fold thickness data available on these children. In contrast to the early, transient effects of diarrhea on height and weight in this study sample, the lasting correlation of early childhood diarrheal illnesses on later physical fitness is not explained by an effect on muscle area or on nutritional status. It is also not explained by anemia or intestinal helminthic infection. This is true even though helminth infections in these children are associated with significant long-term shortfalls in nutritional status (Moore SR, unpublished data). All cryptosporidial infections (6 with diarrhea and 3 without diarrhea), as well as diarrhea were each separately and significantly associated with reduced fitness, albeit not independent of each other in multivariate analysis. Interestingly, while cryptosporidial infections are usually associated with diarrhea in our cohort children, studies in Peru suggest that asymptomatic cryptosporidial infections are even more common, yet still associated with nutritional shortfalls.[34,35] We have not seen other parasites such as *D. fragilis* or microsporidial infections in these children (Lima AAM and others, unpublished data), even though we found the latter in patients with acquired immunodeficiency syndrome in the Statewide Infectious Diseases Hospital 1 block from this community.[36] As noted in the results, shigellosis in 5 of these children, pneumonia in 12, and all other symptoms (mostly upper respiratory and skin ailments) were not correlated with fitness impairment. Controlling for them did not alter the association between early childhood diarrhea and reduced fitness. Limited numbers do not permit separate analyses for other potential enteric pathogens; non-infectious diarrhea seems to be minor in this setting since 82–88% of childhood diarrhea in this cohort is associated with 1 or more potential pathogens (Lima AAM and others, unpublished data). Not surprisingly, early childhood enteric infections with *Cryptosporidium* do co-vary with diarrhea in correlating with later reductions in fitness. Indeed, we and others have found that such enteric infections with *Cryptosporidium* and enteroaggregative *E. coli* can have nutritional effects even without causing overt diarrhea.[23,34,35] These current studies suggest that early childhood *Cryptosporidium* infections (like diarrheal illnesses) are also associated with physical functional defects 4–7 years later in life. These findings suggest that while nutritional status may recover to some extent with reduced diarrhea rates in later childhood, the effects on physical fitness do not recover and may represent a lasting functional impairment in these children. This is the first study of which we are aware that examined these long-term functional correlates with early childhood diarrhea.

From the regression equation, we estimate that a child with 56 days of diarrhea in the first 2 years of life (the average diarrhea burden in the first 2 years of life for this sample) would have a fitness score of 97.1 (95% CI = 92.8–100.6), a significant decrease of 4% from 101.2, the estimated fitness score of a child with no diarrhea in the first 2 years of life. In addition, 3 children with greater than 100 days of diarrhea over the first 2 years of life ($>$ 13.7% of days of life were days with diarrhea) had a mean reduction of 8.2% in their fitness scores. In comparison, the study by Stephenson and others[11] in Kenya showed a increase of 6.9% in fitness scores (using the Harvard Step Test) 4 months after treatment with albendazole for helminth infections. Furthermore, this range of long-term fitness impairment, if persistent, may be associated with substantial reductions in future work productivity. A randomized, controlled trial in Zimbabwe showed that workers treated for schistosomiasis experienced a mean 4.3% increase in Harvard Step Test fitness scores and were 16.6% more productive in their daily job of cutting sugar cane.[37] Thus, the association of early childhood diarrhea with fitness may extend to hampered potential work productivity. Because of the documented secular improvement in nutritional status and diarrhea rates over this study period in these children (Moore SR, unpublished data), these findings represent a best case scenario. Finally, increased physical fitness is clearly associated with fewer illnesses,[38] better health and longevity,[39] and an improved quality of life.[40]

In addition, pilot studies in these children also suggest a prolonged impact of early childhood diarrhea on visual-motor coordination, auditory short-term memory and information processing, and cortical cognitive function as measured by the McCarthy Draw-A-Design, the WISC-III backward digit span, and the WISC-III coding tasks, as summarized in Table 2. Conversely, the forward digit span correlated with activity scores, and prospective problem solving (as determined by the WPPSI-R mazes) correlated with nutritional status (height-for-age Z scores), but not with diarrhea rates, as shown. Clearly, the complexity of these profound effects on functional impairment require and deserve further attention and study.

Several potential limitations should be noted. Most importantly, because of its small size, this study must be seen as provocative but preliminary. The sample size, while sufficient to demonstrate a significant association between early childhood diarrhea and poorer fitness and cognitive function (even largely independent of current nutritional status, anemia, or intestinal helminth infections), was insufficient to allow us to adequately control for all possible confounders. Since the participants in this study (all children with consenting parents born in this cohort) were from the same 5-block community, the entire group served as its own controls, i.e., we examined diarrheal (and other) illnesses in these children, whose diarrheal burdens were spread over the entire range from 1 to 29 episodes in their first 2 years of life. We have controlled for other illnesses, water supplies, sanitation, maternal education, and monthly income and the association of diarrhea with fitness shortfalls have held. However, these factors, as well as specific infections (other than cryptosporidiosis), may well have important, perhaps smaller, component effects. Even though our findings suggest that overall diarrheal illnesses have the greatest correlation, further studies should help define potential contributions of these other factors. Further data are also needed to determine the reproducibility of tests of physical and cognitive function in these children. Whether these various effects are occurring via a recognized effect on micronutrients[41] or can be reversed with targeted antimicrobial, micronutrient, and/or oral rehydration and nutrition therapy remains to be determined, and will be the focus of our future studies. Finally, proof of direct causal linkage of diarrhea or specific enteric infections with functional deficits would require extended studies of targeted interventions as we are now planning.

We conclude that early childhood diarrhea is associated with subsequent impaired physical fitness, and in pilot studies, impaired cognitive function in a long-term cohort follow-up in northeast Brazil. While such an association does not constitute proof of causality, the additional correlation of episodes of diarrhea and of *Cryptosporidium* infections with reduced fitness further strengthens the associations of early childhood diarrhea and *Cryptosporidium* infections with later fitness impairment. Not only will confirmation of these findings and study of potential interventions be crucial in dissecting the causal and pathogenic relationship of early childhood diarrhea and subsequent, long-term functional effects, but such interventions have the potential for a huge, cost-effective impact on improved health and productivity among those in greatest need.

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Authors' addresses: David I. Guerrant, Department of Health and Sports Science, University of Richmond, Richmond, VA 23173. Sean R. Moore, and Richard L. Guerrant, Division of Geographic and International Medicine, University of Virginia School of Medicine, HSC #485, Charlottesville, VA 22908. Aldo A. M. Lima, Department of Physiology and Pharmacology, Clinical Research Unit, Federal University of Ceará, Av. José Bastos, 3390–Sala 90, Porangabussu, Fortaleza, CE, 60.436-160 Brazil. Peter D. Patrick, Department of Pediatrics, University of Virginia School of Medicine, Charlottesville, VA 22908. John B. Schorling, Division of Geographic and International Medicine, and Division of General Medicine, Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA 22908.

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