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Early Childhood Diarrhea Predicts Cognitive Delays in Later Childhood Independently of Malnutrition

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Abstract. Understanding the complex relationship between early childhood infectious diseases, nutritional status, poverty, and cognitive development is significantly hindered by the lack of studies that adequately address confounding between these variables. This study assesses the independent contributions of early childhood diarrhea (ECD) and malnutrition on cognitive impairment in later childhood. A cohort of 131 children from a shantytown community in northeast Brazil was monitored from birth to 24 months for diarrhea and anthropometric status. Cognitive assessments including Test of Nonverbal Intelligence (TONI), coding tasks (WISC-III), and verbal fluency (NEPSY) were completed when children were an average of 8.4 years of age (range = 5.6–12.7 years). Multivariate analysis of variance models were used to assess the individual as well as combined effects of ECD and stunting on later childhood cognitive performance. ECD, height for age (HAZ) at 24 months, and weight for age (WAZ) at 24 months were significant univariate predictors of the studies three cognitive outcomes: TONI, coding, and verbal performance ($P < 0.05$). Multivariate models showed that ECD remained a significant predictor, after adjusting for the effect of 24 months HAZ and WAZ, for both TONI (HAZ, $P = 0.029$ and WAZ, $P = 0.006$) and coding (HAZ, $P = 0.025$ and WAZ, $P = 0.036$) scores. WAZ and HAZ were also significant predictors after adjusting for ECD. ECD remained a significant predictor of coding (WISC III) after number of household income was considered ($P = 0.006$). This study provides evidence that ECD and stunting may have independent effects on children's intellectual function well into later childhood.

INTRODUCTION

Global mortality among children under 5 years of age exceeds 10.6 million each year. Diarrheal illnesses alone account for 1.9 million (18%) of this annual mortality, and 1.2 million (61%) of these deaths are associated with malnutrition.[1–3] Despite improvements in the rates of child mortality in the developing world, the lasting disability due to malnutrition and diarrhea burdens early in life is still greatly underestimated.[4]

Early childhood diarrhea (ECD), defined as diarrheal illness (≥ 3 unformed stools per day) in the first 2 years of life, has been linked to malnutrition-related growth deficits at 24 months of age, and these often remain well into childhood.[5,6] ECD occurring before 2 years of age has also been linked to cognitive deficits that manifest many years later when children reach school.[7–9] Malnutrition has been linked to cognitive functioning.[10] One study found that malnutrition in early childhood was more closely associated with children's Wechsler intelligence quotient (IQ) (a single global measure of intellectual functioning) than either ECD or parasitic infection.[11]

Early weaning coupled with lack of sanitation and impoverished living conditions increase the likelihood of enteric infections in the first 2 years of life. A recent interventional study found that intensive handwashing promotion increased developmental scores in young children.[12] Events critical to developing normal cognitive functioning occurs in young children, including synaptogenesis and neural circuitry myelination in the central nervous system.[13] During the first postnatal years, the developing brain increasingly requires critical nutrients such as zinc, iron, and fatty acids.[14] Intestinal barrier dysfunction and mucosal injury may occur at this time due to various etiologies that may or may not involve overt diarrhea.[6,15] Such clinical or even subclinical illness may limit the overall nutrient supply to the brain.

Though ECD may cause impaired physical growth, many children with severe ECD do not suffer from growth deficits. Our research group has investigated various host and pathogen genetic factors as possible explanations for this phenomenon.[16,17] Long-term cognitive outcomes from ECD and malnutrition are likely to be genetically influenced,[18–21] although these relationships are still incompletely understood.

The purpose of this study is to examine the relationship between ECD, malnutrition, and cognitive deficits. Few studies have examined whether the effect of ECD on specific cognitive domains is best explained by the detrimental effects of diarrhea on growth and nutrition, which then lead to cognitive deficits, or whether ECD alone is a risk factor for these subsequent cognitive deficits. This study addresses this important question regarding the interdependent and independent effects of ECD and poor nutrition on cognitive development.

METHODS

Population. The dataset was obtained retrospectively from a Brazilian cohort of children under active surveillance for

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diarrheal illnesses from 0 to 24 months, living in Gonçalves Dias (GD) shantytown (population approximately 1,800), described in greater detail elsewhere,[22] and are an extension of an initial report of the first 47 children.[7] GD is located in Fortaleza (population estimated at 2.1 million), capital city of the state of Ceará (population approximately 6 million) in northeast Brazil. The GD cohort includes sociodemographic and health surveillance data obtained by study health workers during thrice weekly household visits. Cognitive scores and diarrhea surveillance were obtained from 131 children. Among these children, 56.5% (74/131) were reported upon in two other studies. An initial study examined the relationship between cognitive scores and ECD,[7] while a second assessed the relationship between ECD and school achievement.[8] Neither study attempted to assess the independent effect of ECD from that of nutritional status.

Diarrhea surveillance. We have used the World Health Organization (WHO) guidelines to define a case of diarrhea, as described by Moore and others.[5] Briefly, "diarrhea" was defined as three liquid stools in the preceding 24-hour period. An "episode of diarrhea" was defined as diarrheal illness lasting 1 day and separated from another episode by 48 hours without diarrhea. Overall, study children had 92.7% of their first 730 days of life with observations documented (median = 99.0%; minimum= 42.0%, and maximum = 100.0%). Approximately 10·5% of the sample had fewer than 60.0% of their days with observations recorded. These children were included in our primary analyses to maximize representativeness of the community for whom we were able to obtain cognitive tests 3.6–10.7 years after diarrhea observations were made. Diarrhea surveillance varied in completeness, and the number of episodes over 2 years was estimated using the following formula: (number of diarrhea episodes recorded in the first 24 months of life/number of days observed in first 24 months of life) × 730 days = estimated number of episodes in first 24 months of life. In addition, a secondary set of analyses were conducted on data with children with more than 90% diarrhea surveillance ($N = 106$).

Given the high rate of diarrhea in the GD community, it is not feasible to find a group with no diarrhea to contrast with a group having diarrhea. The median number of episodes of diarrhea experienced by children in this community before they reached the age of 24 months was 5.0 with a mean of 7.16 (standard error [SE] = 0.21; minimum = 0 and maximum = 29). The average duration of the episodes was 3.33 days (median = 3.04; range = 1–7.50). Children with more episodes experienced a somewhat longer durations ($r = 0.24$, $P < 0.01$). For bivariate analyses, the sample was divided into two groups: those with a "low diarrhea burden" (≤ 5 episodes) and those with a "high diarrhea burden" (> 5 episodes).

Anthropometric. Anthropomorphic measurements were used to assess nutritional status; specifically weight-for-age (WAZ) and height-for-age (HAZ) z scores were obtained to evaluate children growth and nutritional status. Anthropometric assessments were completed at birth and at 24 months. The Centers for Disease Control and Prevention 2000 standards were used to calculate z scores for these measurements. We maintained the same z score references used in the previously published articles using the original cohort from GD although WHO 2006 standards were also available. The distribution of children's 24-month anthropometry was: HAZ > −1.00 in 55.6% ($N = 70/126$), HAZ −1.00 to −1.99 in 28.6% ($N = 36/126$), and HAZ ≤ −2.00 in 15.6% (20/126); WAZ > −1.00 in 60.8% ($N = 77/127$), WAZ −1.00 to −1.99 in 29.1% ($N = 37/127$), and WAZ ≤ −2.00 in 10.2% (13/127). The mean 24−month HAZ was −0.68 (SE = 0.10; range = −3.82 to 2.41) with a median of −0.70; while mean 24-month WAZ was −0.88 (SE = 0.10; range = −3.51 to 1.88) with a median of −0.75. HAZ or WAZ values less than or equal to −1.0 (i.e., height or weight below the 15.9th percentile, respectively) were presumed to indicate at least moderate levels of malnutrition.

Cognitive data. Cognitive function was assessed using the standard established by Patrick and others.[9] Three subtests were conducted: verbal fluency, coding, and Test of Nonverbal Intelligence, Third Edition (TONI III). This testing was performed when the children were an average of 8.4 years of age (range = 5.6–12.7 years). All tests were administered by trained professionals, blinded with regard to the children's diarrhea history. All testing was conducted in Portuguese.

Tests of phonetic and semantic fluency were adapted from the NEPSY Developmental Neuropsychological Assessment. Phonetic fluency was assessed by having the child name as many words that begin with "F" and "S" in separate 1-minute trials. Each word was awarded 1 point with no points given for proper names, duplicate words, nonsense words, or words differing only by tense. Semantic fluency was determined by having the child name as many animal species and fruit names in separate 1-minute trials.

The coding test was administered according to the standard Wechsler Intelligence Scale for Children (WISC-III).[23] This test involves paired symbol recall in which the child must remember symbols mapped to corresponding digits. The child was then asked to draw the corresponding symbols for a series of digits. Points were assigned according to the number of correctly drawn symbols (with some leniency for imperfectly rendered symbols). The coding subtest scores the total number of errors in a 120-second trial and the number of correctly drawn symbols at each 30-second interval. The raw test score was converted to a scaled score according to the WISC-III standard. This task assesses three aspects of cognitive functioning: psychomotor speed, concentration, and motor coordination.

Since no Brazilian age standards were available for these tests, raw cognitive scores were adjusted by child age using U.S. standards.

Statistical analyses. Descriptive statistics included mean, standard deviation, and range or percentages for all outcomes, predictors, and covariates as appropriate. As stated previously, the children were divided into two groups: those above the 50th percentile for episodes of ECD (high) and those at or below the 50th percentile (low). The t tests for each of the cognitive scores were used to compare mean differences in cognitive scores for the two groups. Similarly, t tests were also used to compare cognitive scores for children with HAZ scores less than −1.0 and those with HAZ −1.0 or better. The same analyses were performed for children using WAZ scores less than −1.0 compared to those with WAZ −1.0 or better. Two one-way analysis of variance (ANOVA) models were then constructed to determine whether ECD remained a significant contributor to each of the three cognitive outcomes; the first took into account HAZ at 24 months

and the second WAZ at 24 months. Interaction terms were included in the models to assess whether ECD and anthropometry scores had a combined effect on cognitive deficits. Family background including number of household incomes (defined as 1 = 1 minimum wage ranging from US$100 to US$150 per month at the time of testing), maternal education, child sex, child birth weight, and percent days of exclusive breastfeeding in the first year of life was included as a covariate in ANOVA models if any of these variables were related to cognitive outcomes at $P < 0.10$. Linear analyses were conducted using Pearson correlations and regression was used to assess the independence of predictors of cognitive performance.

RESULTS

Household characteristics of children from GD have been described in detailed elsewhere.[24] Table 1 shows child and family characteristics by level of ECD. There were no statistically significant differences in any child or family characteristics. Girls were somewhat less likely than boys to experience heavy ECD.

We compared cognitive performance (TONI III, verbal fluency, and coding scores) for children based on ECD, HAZ, and WAZ, all at 24 months (see Table 2). All three measures were significant ($P < 0.05$) predictors of cognitive performance. Children in the top 50th percentile for ECD (median > 5 episodes) before 24 months had significantly lower TONI, verbal, and coding scores by the time they reached school age. Children with below average growth ($z \leq -1.00$) at 2 years of age also had lower scores. One notable exception was that HAZ at 24 months was not significantly related to children's later verbal performance ($P = 0.108$). In addition, ECD was negatively correlated with growth for both HAZ ($r = 0.23$, $P = 0.011$, $N = 125$) and WAZ ($r = -0.19$, $P = 0.030$, $N = 126$) at 24 months.

ANOVAs were calculated to assess the effect of ECD adjusted for growth shortfall at 2 years; first for HAZ (Model 1) and second for WAZ (Model 2), see Table 3. TONI scores remained significantly lower among children in the top 50th percentile for ECD (median > 5 episodes), even when HAZ and WAZ at 24 months were considered (adjusted $P = 0.029$, $N = 105$ and adjusted $P = 0.006$, $N = 106$, respectively), see Table 3. Heavy diarrhea in the first 24 months resulted in a deficit of approximately 5 points in TONI scores after adjusting for the effect of ECD. ECD occurring in the first 24 months of life also remained a significant (adjusted $P = 0.025$, $N = 89$ and adjusted $P = 0.036$, $N = 90$) and independent predictor of lower coding scores, even once growth shortfalls at 24 months was taken into account. Among all possible covariates, only the number of household incomes was significantly related to coding and so was included as a covariate in the ANOVA for which coding was the dependent variable. ECD did remain a significant predictor of coding after number of household incomes was included ($P = 0.006$) in the ANOVA model.

Table 1

Child characteristics and family demographics described by low (≤ 50th percentile) or high (> 50th percentile) ECD

Cohort characteristics	Low ECD (24 months)	High ECD (24 months)	*P* value
Sex ($N = 137$)			
Female ($N = 83$)	55.4%	44.6%	0.09
Male ($N = 54$)	40.7%	59.3%	
Birth anthropometrics ($N = 132$)			
HAZ	−0.14 ± 0.18	−0.03 ± 0.11	0.59
WAZ	−0.51 ± 0.10	−0.39 ± 0.11	
Days breastfed in first 6 months ($N = 115$), mean ± SE	22.9 ± 0.02	19.1 ± 0.03	0.26
Maternal education ($N = 87$), mean ± SE	1.7 ± 0.17	1.7 ± 0.20	0.83
Monthly income† ($N = 123$), mean ± SE	5.0 ± 0.25	5.3 ± 0.29	0.42

ECD = early childhood diarrhea; HAZ = height-for-age *z* score; SE = standard error; WAZ = weight-for-age *z* score.
†One minimum wage ranging from US$100 to US$150 per month at the time of the test.

Table 2

Mean differences and standard deviation of in cognitive scores based on ECD before 24 months and malnutrition (HAZ and WAZ) at 2 years of age

	TONI scores mean (±sd)	*P* value	Verbal scores mean (±sd)	*P* value	Coding scores mean (±sd)	*P* values
ECD	$N = 111$		$N = 131$		$N = 97$	
High	82.5 (9.0)		5.0 (3.0)		5.3 (3.3)	
Low	86.9 (8.7)	0.010	6.2 (3.3)	0.038	6.8 (3.7)	0.027
HAZ	$N = 105$		$N = 119$		$N = 89$	
≤ −1.00	82.2 (7.2)		5.0 (3.2)		4.4 (3.5)	
> −1.00	85.9 (10.1)	0.043	5.9 (3.2)	0.108	6.6 (3.3)	0.004
WAZ	$N = 106$		$N = 120$		$N = 90$	
≤ −1.00	81.8 (7.6)		4.5 (3.2)		4.5 (3.4)	
> −1.00	86.3 (9.8)	0.015	6.2 (3.0)	0.005	6.6 (3.4)	0.005

ECD = early childhood diarrhea; HAZ = height-for-age *z* score; TONI = Test of Nonverbal Intelligence; WAZ = weight-for-age *z* score.

Secondary analyses were performed to assess whether completeness of observations within the first 24 months of life would affect our results. The number of episodes of diarrhea was similar for children with greater than 90% observation (mean = 7.8, median = 5, range = 0–29, $N = 106$) compared with all children in the study cohort (mean = 7.6, median = 5, range = 0–29, $N = 135$). Univariate and multivariate models with ECD and growth as predictors of cognitive performance also showed similar results to that of the complete cohort. In fact, analyses conducted using this cohort with more complete ECD surveillance revealed an even stronger relationship between ECD and all three measures of cognitive performance.

TONI scores were again significantly lower for children with the greatest diarrhea burdens (i.e., top 50th percentile for ECD [median > 5 episodes]) when compared with those with lower burdens (i.e., bottom 50th percentile for ECD [median ≤ 5 episodes]) ($P = 0.009$, $N = 105$). This remained true after HAZ ($P = 0.025$, $N = 91$) and WAZ ($P = 0.011$, $N = 92$) at 24 months was included in the ANOVA as covariates. Verbal scores were significantly lower for children with the greatest diarrhea burden (i.e., top 50th percentile for ECD [median > 5 episodes]) when compared with those with less burden (i.e., bottom 50th percentile for ECD [median ≤ 5 episodes]) ($P = 0.004$, $N = 106$), although this was not true when children with less complete surveillance were included in this analysis. This remained true after HAZ ($P = 0.009$, $N = 100$) and WAZ ($P = 0.022$, $N = 101$) at 24 months were included in the ANOVA as covariates. The ECD and WAZ at 24 months interaction term included in the ANOVA nearly reached statistical significance ($P = 0.093$, $N = 101$). Children with the greatest diarrhea burden (i.e., top 50th percentile for ECD [median > 5 episodes]) and near normal

TABLE 3

Multivariate comparison of ECD and malnutrition at 2 years of age as adjusted predictors of later cognitive scores with coefficient effect size and model R^2

	TONI scores	Adjusted *P* value	Verbal scores	Adjusted *P* value	Coding scores	Adjusted *P* value
Model set 1: ECD and HAZ						
	(Model $R^2 = 0.09$, $P = 0.01$)		(Model $R^2 = 0.06$, $P = 0.09$)		(Model $R^2 = 0.15$, $P = 0.01$)	
ECD			($N = 105$)			
High	82.2 (9.2)	0.029	4.8 (2.9)	0.056	5.0 (3.2)	0.025
Low	86.7 (8.6)		6.1 (3.3)		6.6 (3.7)	
HAZ						
≤ −1.00	82.2 (7.1)	0.089	5.0 (3.2)	0.185	4.4 (3.5)	0.009
> −1.00	85.9 (10.1)		5.9 (3.2)		6.6 (3.3)	
ECD by HAZ						
High						
≤ −1.00	80.9 (8.4)	0.758	4.8 (2.9)	0.177	3.4 (2.1)	0.230
> −1.00	83.4 (9.9)		4.8 (2.9)		6.2 (3.4)	
Low						
≤ −1.00	84.3 (3.8)		5.2 (3.4)		5.9 (4.5)	
> −1.00	87.9 (10.0)		6.7 (3.2)		7.0 (3.1)	
Model set 2: ECD and WAZ						
	(Model $R^2 = 0.11$, $P = 0.002$)		(Model $R^2 = 0.12$, $P = 0.002$)		(Model $R^2 = 0.14$, $P = 0.005$)	
ECD			($N = 106$)			
High	82.2 (9.2)	0.006	4.8 (3.1)	0.092	5.0 (3.2)	0.036
Low	87.0 (8.7)		6.1 (3.3)		6.7 (3.6)	
WAZ						
≤ −1.00	81.8 (7.6)	0.037	4.5 (3.2)	0.008	4.5 (3.4)	0.021
> −1.00	86.3 (9.8)		6.2 (3.0)		6.7 (3.4)	
ECD by WAZ						
High						
≤ −1.00	78.6 (5.5)	0.116	4.4 (3.1)	0.144	3.6 (3.2)	0.251
> −1.00	85.1 (10.6)		5.1 (2.7)		6.2 (3.4)	
Low						
≤ −1.00	86.4 (8.0)		4.6 (3.3)		6.1 (4.5)	
> −1.00	87.3 (9.1)		6.7 (3.0)		7.0 (3.3)	

ECD = early childhood diarrhea; HAZ = height-for-age *z* score; TONI = Test of Nonverbal Intelligence; WAZ = weight-for-age *z* score. Standard deviation values are given in parentheses.

or normal growth (WAZ > −1) had the highest TONI scores. Children with low weight (WAZ ≤ −1) at 24 months demonstrated lower verbal performance whether they had suffered diarrhea, while near normal to normal weight children had equally low verbal performance scores if they suffered the heavy diarrhea burdens.

Coding scores were again significantly lower for children with the greatest diarrhea burden (i.e., top 50th percentile for ECD [median > 5 episodes]) when compared with those with less burden (i.e., bottom 50th percentile for ECD [median ≤ 5 episodes]) ($P = 0.023$, $N = 88$). This remained true after HAZ ($P = 0.030$, $N = 82$) and WAZ ($P = 0.036$, $N = 83$) at 24 months was included in the ANOVA as predictors.

Pearson correlations in Table 4 show linear associations among cognitive scores, diarrhea, and growth status. TONI IQ and verbal scores are significantly correlated with 24-month HAZ/WAZ and ECD. Coding scores are significantly correlated with growth status only (24 month HAZ/WAZ). Linear regression analyses with 24-month HAZ and ECD showed that only growth was an independent predictor of cognitive scores.

Differences in verbal scores appeared to primarily occur as a result of poor WAZ at 24 months when children with less complete diarrheal surveillance were included in the analyses. The ANOVA model fit improved after family income was included in the model as a covariate, making the interaction term statistically significant ($P = 0.030$), although missing data limited our ability to assess these covariates. Our dichotomized analyses suggest a direct effect of ECD on later cognitive performance that was not accounted for the effect of measurable growth shortfalls.

DISCUSSION

The vicious cycle of malnutrition and diarrhea in the most formative 2 years of neurological development has profound and lasting impact on children's growth, school performance, and cognitive development.[6,7,24] In malnourished children, exposure to multiple bouts of diarrheal illnesses may impair intestinal function in two ways. First, repeated enteric damage may lead to villus feathering and reduced absorptive surface.[25,26] Second, repeated diarrheal illnesses may further alter intestinal function in children by disrupting the intestinal epithelial barrier, an effect that may also trigger intestinal inflammation.[27,28] Importantly, these effects have been shown to be reversible with nutritional interventions.[29]

While the apparent reversibility of the intestinal effects of diarrhea is encouraging, evidence shows that the influence of the disease (with potentially reduced nutrient availability) on the developing brain may be less amenable to later intervention. Although several studies have documented the lasting impact of repeated enteric illnesses (even without overt diarrhea) on growth faltering in children,[30,31] especially those with early onset and heaviest loads,[1,32] the compound and isolated effects of diarrhea, with or without growth deficits, on children's cognitive development are not well understood. Stunting (or reduced height for age) has been consistently identified as one of the best markers to predict cognitive deficits later in life, although stunting may simply be a surrogate

TABLE 4
Simple Pearson correlations between all cognitive scores, anthropometry, and diarrheal illness

		TONI IQ	Coding	Verbal	ECD under 24 months	Percentage of DoD under 24 months	HAZ at 24 months	WAZ at 24 months
TONI IQ	*r*	1	0.309†	0.557†	−0.222*	−0.173	0.231*	0.239*
	p		0.004	0.000	0.019	0.077	0.018	0.014
	n	111	86	107	111	105	105	106
Coding	*r*		1	0.381†	−0.127	0.016	0.251*	0.239*
	p			0.000	0.214	0.876	0.018	0.023
	n		97	95	97	94	89	90
Verbal	*r*			1	−0.202*	−0.103	0.140	0.188*
	p				0.021	0.254	0.130	0.040
	n			131	131	124	119	120
ECD for children under 24 months	*r*				1	0.804†	−0.229*	−0.197*
	p					0.000	0.010	0.027
	n				137	130	125	126
Percentage of DoD under 24 months	*r*					1	−0.090	−0.023
	p						0.331	0.802
	n					130	118	119
HAZ at 24 months	*r*						1	0.714†
	p							0.000
	n						126	126
WAZ at 24 months	*r*							1
	p							
	n							127

ECD = early childhood diarrhea; DoD = days of diarrhea; HAZ = height-for-age *z* score; IQ = intelligence quotient; *n* = sample size; *p* = *P* value; *r* = correlation coefficient; TONI IQ = Test of Nonverbal Intelligence; WAZ = weight-for-age *z* score.
*Correlation significant at the 0.05 level.
†Correlation significant at the 0.01 level.

for ECD or asymptomatic enteric pathogen or helminthic infections.[33,34] Beyond statistical significance level, it is important to note that the differences that approach 10 points on a 100-point standardized cognitive test are often considered to be an important difference in cognitive performance.[35] Our interaction effect results do show that a child suffering from both a higher number of ECDs and stunting is 7–9 TONI points lower than those suffering from neither.

Although, the specific pathogenic effect from distinct diarrhea etiologies on cognitive development has not been elucidated (and is not assessed in this article), the load of the enteric infections as reflected by symptomatic diarrhea (quantified according to duration, early onset, and number of episodes) has been consistently related to reductions in cognitive scores.[7,9] Although heavy diarrheal illness burdens in the first 2 years of life lead to impaired physical growth, subsets of children afflicted with the same burdens of diarrhea at 2 years of age (as those with APOE4 alleles) have spared cognitive impairment.[20] Conversely, current data indicate that diarrheal illnesses lead to cognitive deficits even in the absence of effects on physical growth parameters. We suggest that ECD effects on cognitive development are both dependent on and independent of growth. This could occur due to intestinal disruption that affects growth and growth signaling and in turn cognition or potentially through systemic inflammatory signals that may be independent of growth signaling, as has been suggested by other studies.[36,37] In this study, we have shown that stunting and diarrheal illnesses can independently disrupt normal cognitive development. The explanation of the effect of diarrhea per se in reducing cognitive scores may relate to intestinal inflammation and potential damaging cytokines or impaired absorption of nutrients that are more critical to neural development than to physical growth. Conversely, however, the effect of stunting without overt diarrhea does not necessarily preclude the importance of enteric infections on cognitive development without diarrhea, since stunting may also occur with "asymptomatic" enteric infections. These "asymptomatic" enteric infections may also be associated with subclinical changes in intestinal barrier and absorptive function or may compete for nutrient absorption.[38] Inflammatory responses due to chronic or subclinical infestations might trigger damaging cytokine release or otherwise jeopardize nutrient transport and alter electrolytic and water balance, without major significant effects on physical growth. Alternatively, of course, malnutrition may also relate to inadequate dietary intake (with or without enteric infection). Differences in verbal scores appear to correlate best with a poor WAZ at 24 months. Interestingly, a critical time for developing speech fluency in children occurs at 8–12 years of age, the same approximate time of our cognitive assessments,[39] when they rely on myelinated neural pathways. Such pathways are largely developed during early childhood with the aid of lipids and other nutrients.[40] Coding and TONI scores were found to be consistently affected by ECD, as previously shown in our initial studies in a subset of these children.[8]

Limitations of this study include our single site in Brazil and a relatively moderate number of children for whom we were able to obtain 4- to 7-year follow-up for this multivariate analyses. Another limitation is the limited cross-cultural validation of cognitive tests done. Strengths include the long-term intense follow-up of a birth cohort, with complete data on factors hypothesized to be associated with IQ, a battery of tests for different aspects of cognitive function, and community level data on the relationship of specific infections instead of all infections at a national level of estimates.

The profound and lasting impact of under nutrition and ECD remains a major threat to children's cognitive development in impoverished areas throughout the world. Yet the relative contribution of each remains unclear. As understanding these interactions is critical to effective interventions, we have focused on their relative contributions to

cognitive impairment. These results suggest a direct effect of ECD on later cognitive performance that is not accounted solely for the detrimental effect of diarrhea on growth status. Hence, both overt diarrhea and malnutrition (possibly related to covert enteric infections or to inadequate diets or both) in early childhood must be addressed by effective interventions if optimal cognitive development is to be achieved among children in impoverished areas.

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