

Early childhood diarrhoea and helminthiases associate with long-term linear growth faltering

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Background	Although the acute mortality from diarrhoeal diseases is well recognized, the potentially prolonged impact of early childhood diarrhoea on background growth and development is often overlooked. To examine the magnitude and duration of the association of early childhood enteric infections with growth faltering in later childhood, we investigated associations of early childhood diarrhoea (0–2 years) and intestinal helminthiases with nutritional status from age 2 to 7 years.
Methods	Twice-weekly diarrhoea surveillance and quarterly anthropometrics were followed from 1989 to 1998 in 119 children born into a Northeast Brazilian shantytown.
Results	Diarrhoea burdens at 0–2 years old were significantly associated with growth faltering at ages 2–7 years, even after controlling for nutritional status in infancy, helminthiases at 0–2 years old, family income, and maternal education by Pearson correlation, multivariate linear regression, and repeat measures analysis. The average 9.1 diarrhoeal episodes before age 2 years was associated with a 3.6 cm (95% CI : 0.6–6.6 cm) growth shortfall at age 7 years. Early childhood helminthiasis was also associated with linear growth faltering and a further 4.6 cm shortfall (95% CI : 0.8–7.9 cm) at age 7 years.
Conclusions	Early childhood diarrhoea and helminthiases independently associate with substantial linear growth shortfalls that continue beyond age 6 years. Targeted interventions for their control may have profound and lasting growth benefits for children in similar settings.
Keywords	Burden of disease, childhood development, diarrhoea, enteric infections, growth faltering, helminthiasis, malnutrition
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Diarrhoeal disease remains a leading cause of childhood illness and death in developing regions of the world. Global reports of diarrhoeal morbidity and mortality in children under 5 years old in developing countries estimate an incidence of 2.6 diarrhoeal episodes per child-year and a mortality of 1.5–5.1 million deaths per year.^{1–3} In poorer areas of the tropics, however,

illness surveillance has consistently revealed higher diarrhoea attack-rates (up to 19 episodes per child-year).^{4,5} While the staggering child mortality and acute growth faltering resulting from diarrhoeal diseases in developing areas are well studied, relatively little attention has been given to the potential long-term sequelae of repeated malnourishing episodes of diarrhoea in the developmentally critical first years of life.⁶ While 'catch-up' growth occurs following diarrhoeal illnesses,⁷ it is blunted if repeated diarrhoeal illnesses ensue.⁸ Only now are we beginning to recognize the potential long-term effects of early childhood diarrhoea.⁶

The 'vicious cycle' of diarrhoea and malnutrition (in which diarrhoea leads to poorer nutritional status and poorer nutritional status predisposes to further diarrhoea) has long been recognized, but only partially understood.^{6,8–12} Furthermore, the duration of this interaction, e.g. how long the effects of diarrhoea on nutritional status are evident in a child's growth profile, is poorly defined. Issues of catch-up growth after

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diarrhoeal episodes, other infections which affect nutritional status (e.g. helminth infections) during childhood and socio-economic confounders all complicate efforts to untangle this relationship.

Helminth infections are known to impair short-term growth, micronutrient levels, physical fitness, cognitive function, and work productivity.^{13–21} Much of the data on physical and cognitive deficits due to helminths come from randomized control trials of anthelmintics, with outcome measures collected 3 weeks to one year after initiation of treatment or placebo. Attempts to define the long-term growth impact of helminth infections in early childhood are complicated by factors similar to the association between diarrhoea and growth shortfalls: catch-up growth, co-infections (including diarrhoea), and socioeconomic variables.

Studies of sufficient breadth and length to address the question of the duration of the association of early childhood diarrhoea and helminths with growth faltering are few in number. One such study, the Gonçalves Dias longitudinal surveillance project has consisted of diarrhoea and nutritional surveillance of children born into an urban Brazilian shantytown since August 1989.²² Surveillance continued into 1999. From August 1989 to April 1993, the project also included microbiological examination of stools collected regularly from children with and without diarrhoea. The present analysis is based on Gonçalves Dias surveillance data from August 1989 to December 1998 and has two purposes: (1) to define the magnitude and duration of the associations of early childhood diarrhoea and intestinal helminthiasis with nutritional status in later childhood and (2) to examine the independence of these associations (diarrhoea and helminthiasis versus nutritional status) when controlling for nutritional status before one year of age and socioeconomic variables.

Materials and Methods

Study site and subjects

The study site was Gonçalves Dias (population approximately 1800), a shantytown (favela) in Fortaleza (population approximately 2.3 million), capital city of the state of Ceará (population approximately 6 million) in Northeast Brazil. In 1989 Fortaleza's infant mortality ratio was 56/1000/year, which by 1998 had dropped to 21/1000/year (source: Ceará State Secretary of Health). From August 1989 to December 1998, a local field team consisting of two study nurses and two trained community health workers from the local neighbourhood identified all pregnancies in the community, offered the mothers enrolment, 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 and informed consent were approved by the human investigation committees of the Federal University of Ceará and the University of Virginia. Analyses of select pathogens in this and nearby populations have already been reported for *Cryptosporidium*,^{23–25} enteroaggregative *Escherichia coli*,²⁶ torovirus²⁷ and Norwalk virus²⁸ infections; and on overall illness rates and risk factors for persistent diarrhoea.²² Some of the older cohort children have also been studied for physical fitness⁶ and cognitive function in relation to early childhood diarrhoea burdens.

Illness surveillance and nutritional assessment

From August 1989 through April 1993, members of the field team visited each study-home thrice weekly (Monday, Wednesday, Friday) to record diarrhoea since the last visit. Beginning in May 1993, surveillance frequency switched from thrice to twice weekly (Monday, Thursday). We used World Health Organization (WHO) guidelines to define a case of diarrhoea: ≥ 3 liquid stools within a 24-hour period, as noted by caregivers. Distinct diarrhoea episodes were separated by at least 2 days free of diarrhoea. Diarrhoea duration of < 2 weeks was classified as acute diarrhoea; ≥ 2 weeks as persistent diarrhoea.

After training by the investigators and testing for reproducibility (within 0.1 cm length and 0.1 kg weight), the field team measured the length of study children quarterly. Length was measured supine to the nearest 0.1 cm with a measuring board. Length measurements were converted to height-for-age z-scores (HAZ) using anthropometric software (EpiInfo). We used NHANES II referenced data as noted; new NHANES III data are similar. These anthropometric z-scores are the number of standard deviations above or below the median values for the National Center for Health Statistics (NCHS)²⁹ international reference population, approved by WHO³⁰ for international use. In this study, the two scores were used to compare the nutritional status of children from the same cohort with different diarrhoea and helminth burdens in early childhood.

Stool collection and evaluation for helminths

From August 1989 to April 1993, stools were obtained when possible from all diarrhoeal illnesses and triannually from children without diarrhoea. In addition to evaluation for enteric pathogens,²² fecal specimens were examined by wet mount and were concentrated by standard formalin ether methods and stained with iodine for microscopy of ova and parasites. Treatment for documented *Ascaris*, *Trichuris* or hookworm infections, in the form of mebendazole, was provided free through a nearby clinic.

Data analysis

After compiling all diarrhoea surveillance data from August 1989 to December 1998 we identified children with the most complete follow-up during their first 2 years of life (defined as 700 child-days or more of observation; i.e. $> 96\%$ of a possible 730 days). We then calculated the number of episodes, number of persistent episodes, and number of diarrhoea days in their first 2 years of life. We determined *a priori* to use diarrhoea histories from the first 2 years of life for two reasons: (1) access to complete data on a requisite number of children to test our hypothesis that early childhood diarrhoea is associated with long-term growth shortfalls and (2) diarrhoea attack-rates peak in the first 2 years of life in this cohort, as well as others.^{22,31}

Bivariate associations of early childhood diarrhoea with anthropometry at ages 2–7 years were examined by Pearson correlation. Repeat measures analysis was used to compare means of height-for-age z-scores, from ages 2 to 7 years, for children with and without early childhood *Ascaris lumbricoides* or *Trichuris trichiura*, the predominant intestinal helminthic infections seen. Multiple linear regression and repeat measures analyses were used to examine the association of early childhood diarrhoea and helminthiasis across age groups, when

controlling for nutritional status before the age of one year, maternal education (whether or not the mother had completed primary school), and family income (number of minimum salaries per month). Statistical analyses were performed using SPSS-PC version 7.5 (SPSS Inc., Chicago, IL). All tests were two-tailed and P -values < 0.05 were considered statistically significant.

Repeat measures models were used to examine the effects on linear growth of helminthiasis and diarrhoea burden in the first 2 years of life. These models were also used to assess the effects of helminthiasis and diarrhoea burden after adjusting for socioeconomic factors, specific early childhood enteric infections and height-for-age before one year old. In fitting these models, it was assumed that the linear growth measurements have constant variance across the measurement ages and that the correlation between two linear growth measurements from the same child is a decreasing function of the amount of time between the two measurements. Parameters in the models were estimated using restricted maximum likelihood methods (REML).

Results

Of 380 children born into the study during August 1989 to December 1998, 318 were age 2 years by December 1998 and 119 had complete surveillance data (≥ 700 days) during ages 0–2 years and were included in the analysis. The mean number of episodes in the first 2 years of life was 9.1 (SD 6.2) episodes

per child, 0.4 (SD 1.0) persistent episodes per child, and 43.5 (SD 48.7) days of diarrhoea per child (6% of days). The aetiologies and epidemiology of diarrhoea in this cohort are reported elsewhere.²² Of these 119 children, 82 (68.9%) were born before April 1993, the period when stool samples were collected for aetiological studies. These 82 children gave a median number of six stool samples during ages 0–2 years old. Microbiological analyses of these stools showed that 42 (51%) children had intestinal helminths (*Ascaris* in 21, *Trichuris* in 8, both in 13). Only 8 of the 42 children with early childhood helminths were positive in the first year of life. There was no significant difference in the mean number of stools samples taken from children with and without helminths (7.4 and 6.9 samples, respectively). The socioeconomic questionnaires showed that only 22 (18%) of the 119 children came from homes where the mother had completed primary school and 35% (30/87) came from homes with a monthly income < 1 minimum salary (= US\$120/month).

Of the three measures of early childhood diarrhoea burden (number of episodes, number of persistent episodes, days of diarrhoea), number of episodes had the most consistent, significant inverse correlations with height-for-age. The number of episodes before age 2 years had significant inverse correlations with HAZ from age 2 to 6 years (two-tailed $P < 0.01$). Figure 1 shows the plot of early childhood diarrhoea episodes versus HAZ at ages 2–7 years. Children with heavier diarrhoea burdens at 0–2 years tended to be of smaller stature at ages 2 through 7 years. Although the strength of the correlation of early

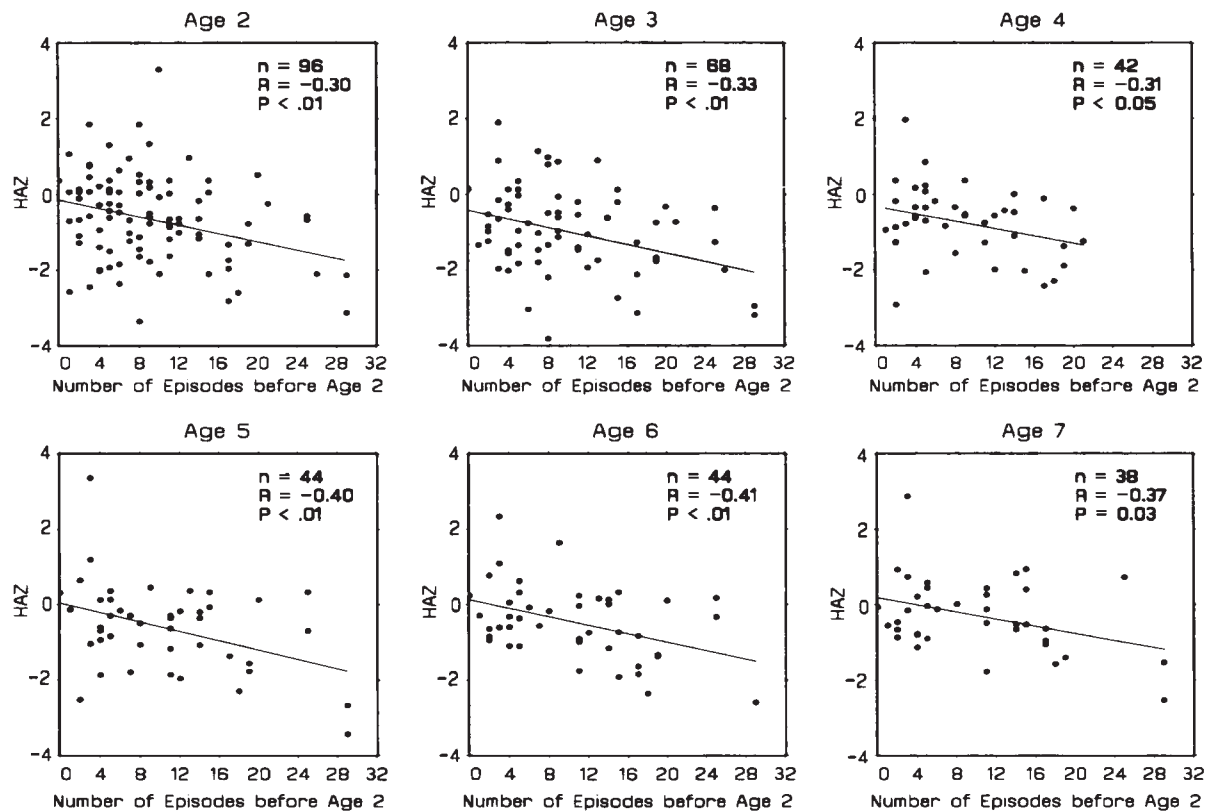


Figure 1 Correlations of numbers of episodes of early childhood diarrhoea prior to age 2 with height-for-age z-scores (HAZ) at ages 2 through 7 years

childhood diarrhoea with nutritional status diminished slightly as children grew older, a significant amount of the variation in HAZ at age 6 was still explained by early childhood diarrhoea ($R^2 = 0.17$, $P = 0.006$).

The correlations suggest that early childhood diarrhoea and HAZ are associated, but these analyses do not take advantage of the longitudinal design of the study. Figure 2 displays the average HAZ by age for children grouped according to the number of episodes of diarrhoea: 0–4, 5–8, 9–12 and >12 episodes. These groupings were chosen to yield approximately equal percentages of children in the four groups (24%, 29%, 22% and 25%, respectively). Although the mean profiles are variable, there are patterns suggested by the profiles. A greater number of diarrhoeal episodes are associated with a greater shortfall in HAZ by age 2. This is followed by an upward trend in HAZ scores for ages 2 through 7, indicating 'catch-up growth' in these children. The rate of catch-up growth appears to be similar across the four groups, although it may be slightly accelerated in the group with the largest number of diarrhoeal episodes. Repeat measures models were used to investigate the patterns suggested by Figure 2. Using the number of episodes as a continuous variable, these models were used to assess the effect of early childhood diarrhoea on (1) changes in mean HAZ prior to age 2 and (2) the rate of catch-up growth in ages 2 through 7 years. The models are based on an assumption, supported by Figure 2, that apart from sampling variation, the average HAZ scores change linearly from ages 2 to 7 years.

Figure 3 shows the model predicted mean HAZ by age for selected values of the number of diarrhoeal episodes. The estimates and confidence intervals are based on the assumption of linear changes in HAZ after year 2; the dotted line displays estimates of the mean HAZ without the assumption of linear changes in HAZ. Figure 4 shows the model-based estimate of the effect of each additional episode on the mean HAZ up to age 8 from the model that assumes linear changes (solid line) and the model that does not assume linear changes in HAZ after age 2 (dotted line). The model indicates that a greater number of diarrhoeal episodes are associated with a lower HAZ from ages 1–2 through ages 5–6 ($P < 0.05$), adjusted for multiple comparisons. It is estimated that each additional episode prior to age 2 is associated with a 0.004 (SE = 0.003, $P = 0.17$, F-test 1,445 d.f.) increase in the slope of the mean HAZ profile after

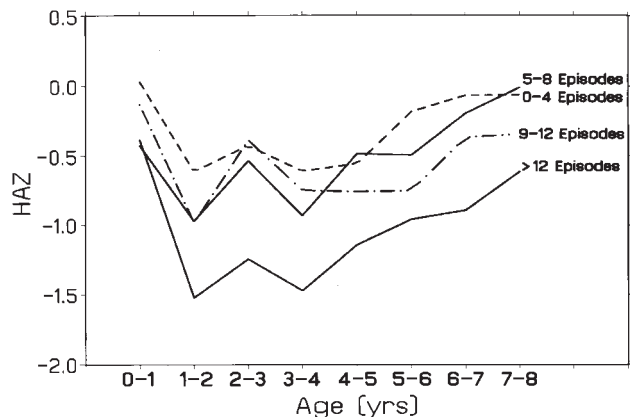


Figure 2 Average height-for-age z-scores (HAZ) by age and number of episodes of diarrhoea in the first 2 years of life

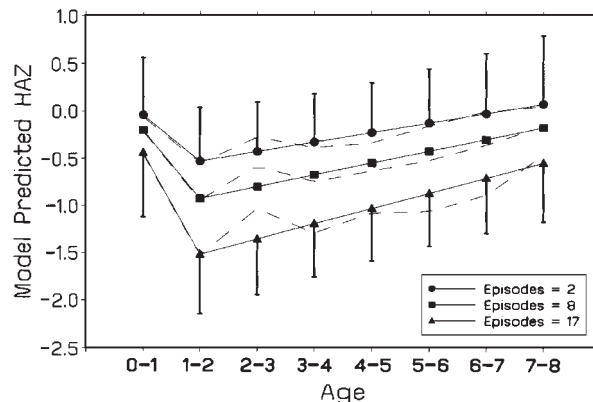


Figure 3 Model-based estimates of mean height-for-age z-scores (HAZ) by age and number of diarrhoeal episodes. The vertical bars indicate half of a 95% simultaneous confidence interval for the mean; the simultaneous intervals were computed using the Bonferroni adjustment

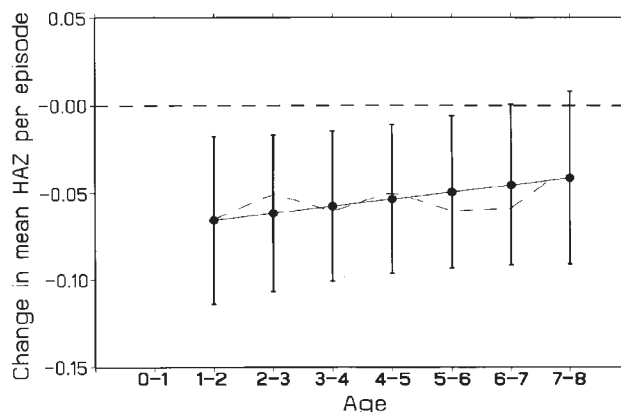


Figure 4 Model-based estimates of the effect of each episode in the first 2 years of life on mean height-for-age z-scores (HAZ) at ages 0–7 years. The vertical lines are simultaneous 95% CI using the Bonferroni multiplier

age 2. This suggests that the rate of catch-up growth is greater among children with a greater number of diarrhoeal episodes, but the estimated effect is not statistically significant. Nearly identical results for the effect of diarrhoeal episodes on HAZ were obtained by analysing HAZ scores from ages 2–7, adjusting for HAZ score in age 0–1, maternal education and family income.

Figure 5 shows the significant differences in mean HAZ scores, from ages 2 to 7 years old, for children with and without a history of early childhood *Ascaris* or *Trichuris*.

Figure 6 displays the model-based estimates of the mean HAZ profiles for children with 2, 8 or 17 episodes of early childhood diarrhoea, with or without helminths. The overall effect of helminths on growth was statistically significant ($F = 2.84$, 6,77 d.f., $P = 0.02$). Figure 6 suggests that, regardless of the number of episodes of early childhood diarrhoea, children with helminths show a steeper decline in HAZ scores prior to age 2 than do children without helminths ($F = 3.33$, 2,77 d.f., $P = 0.04$). The models suggest that the rate of catch-up growth after age 2 among children without helminths is not statistically significant ($F = 0.08$, 1,355 d.f., $P = 0.77$). Figure 6 suggests that, in children

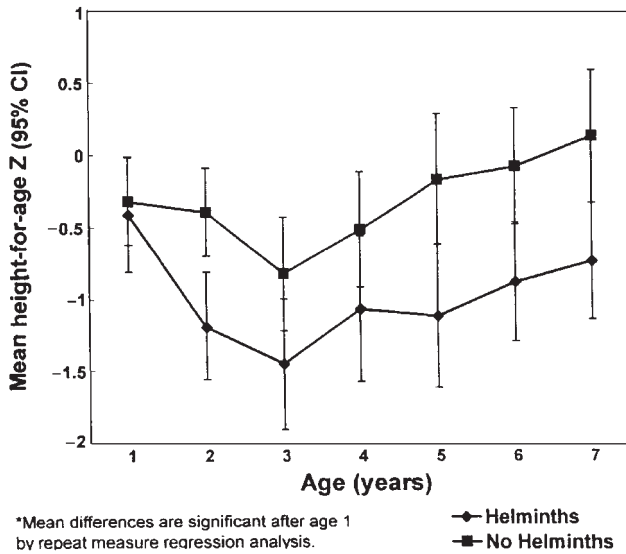


Figure 5 Mean height-for-age z-scores by age in children with (diamonds) and without (squares) intestinal helminths

with helminths, the rate of catch-up growth does not offset the initial decline in HAZ prior to age 2. For example, the mean HAZ at age 7 for children with helminths and eight episodes of early childhood diarrhoea is estimated to be 0.67 units (SE = 0.26), lower than a child with no helminths and eight episodes of early childhood diarrhoea. Similar results for the effects of episodes of early childhood diarrhoea and helminths were obtained by analysing HAZ after age 2, adjusting for HAZ before age one year old, maternal education, and family income. After adjusting for these variables, the average diarrhoea burden of 9.1 episodes before age 2 years old was associated

with a 3.6 cm (95% CI: 0.6–6.6 cm) growth shortfall at age 7 years by multivariable linear regression. After adjusting for these same variables, early childhood helminthiasis was also associated with linear growth faltering and a further 4.6 cm shortfall (95% CI: 0.8–7.9 cm) at age 7 years. Children were also weighed and there were no significant relationships between weight in older childhood and earlier childhood diarrhoea or helminthiasis.

Discussion

In this long-term prospective cohort study we find that both early childhood diarrhoea (0–2 years) and intestinal helminthiasis independently associate with profound and lasting linear growth shortfalls. These associations remain significant when controlling for a number of possible confounders, including nutritional status during infancy, other parasitic infections, diarrhoea in later childhood and socioeconomic variables. To our knowledge, this is the first study to demonstrate growth faltering beyond age 6 years in relation to early childhood diarrhoea burdens and helminthiasis; thus, it has important implications that deserve further study. Furthermore, these effects are seen in a ‘best case’ scenario, since there have been substantial secular improvements with reduced diarrhoea rates and improving nutritional status in these children over the study period (improvements not seen in nearby shantytown children recently surveyed).³¹ While these data cannot assign causality, a causal relationship between early childhood enteric infections and prolonged growth faltering is plausible.⁸

Catch-up growth is the ordinary phenomenon of rapid growth acceleration that occurs in children who have experienced a cause of growth retardation (e.g. diarrhoea) that has recently been removed.^{32,33} Although these children’s mean HAZ scores began to improve after age 3 years (one year after diarrhoea attack rates peak in this cohort²²), catch-up growth

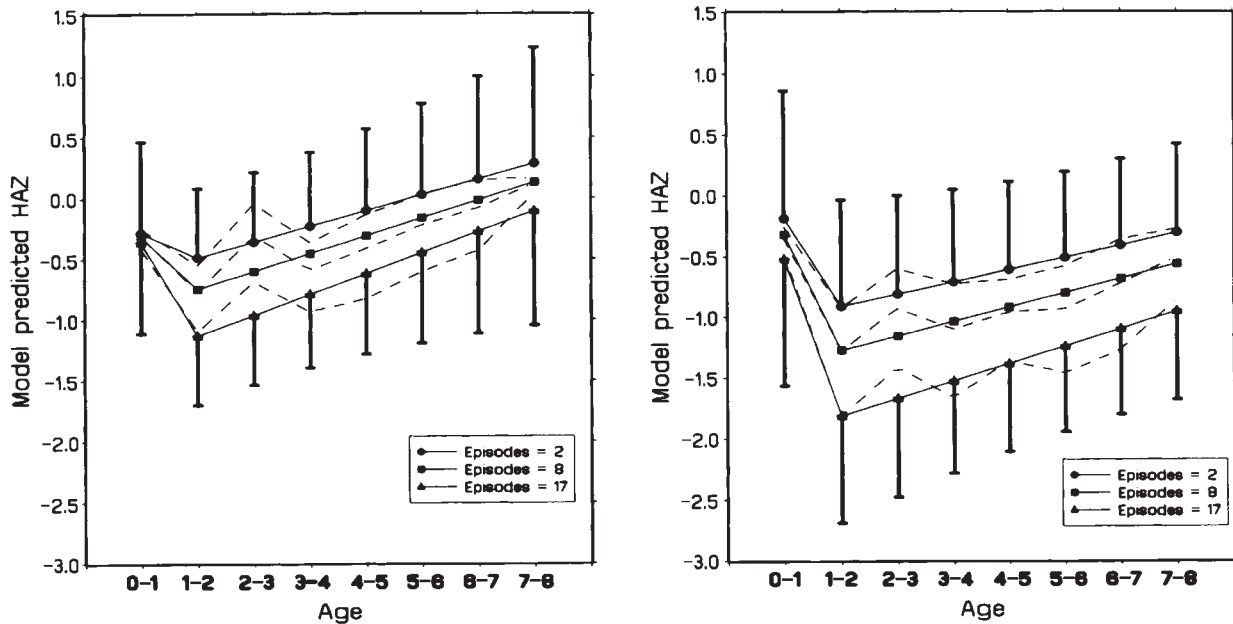


Figure 6 CModel-based estimates of mean height-for-age z-scores (HAZ) by age and helminth status (left panel = no helminths; right panel = helminths) for selected values of the number of episodes of early childhood diarrhoea

did not erase the strong associations of early childhood diarrhoea and helminths with growth shortfalls beyond age 3 years old. Analyses of later heights adjusted for height at one year of age correspond to analyses of growth from age one onward. A previous study in this community, in a different group of children, by Schorling *et al.*⁸ showed that catch-up growth of malnourished children is frequently ablated by further diarrhoea. High diarrhoea attack-rates, as well as a high incidence of other infections in malnourished children, may have ablated complete catch-up growth in children to the degree where associations between children's early childhood diarrhoea and nutritional status were still evident in later childhood.

Specific diarrhoeal pathogens may have played a role. In this cohort, as well as in cohorts from Peru and Guinea-Bissau, investigators found that early childhood cryptosporidiosis led to prolonged stunting.^{25,34,35} Postulated mechanisms were *Cryptosporidium*-induced intestinal injury resulting in persistent malabsorption and enhanced susceptibility to further endemic enteric infections, which offer two potential explanations for the long-term associations between early childhood diarrhoea and long-term linear growth faltering in this cohort. In this study, however, comparison of age 0–7 year growth profiles for children with and without early childhood cryptosporidiosis, did not reveal significant differences—although additional subsequent cryptosporidial infections in these children may have had further effects, and early childhood cryptosporidial infections alone in this population are associated with reduced physical fitness 4–7 years later.⁶

These associations remained significant after controlling for nutritional status in infancy (less than one year old). Early diarrhoea and helminth burdens explain reduced height-for-age in later childhood even after controlling small stature from early childhood.

As with early childhood nutritional status, controlling for socioeconomic indicators (maternal education and family income) did not remove the significance of the association of early childhood diarrhoea and of helminths with impaired growth. These variables were important to control for in these analyses because they have previously been shown to correlate with diarrhoea and nutritional outcomes in this community,¹¹ as well as others. Controlling for these variables may have also served to adjust somewhat for differences in dietary intake, a variable that is otherwise difficult to quantify over long periods at the community level.

Finally, to analyse for any possible selection bias, the baseline characteristics of the 199 infants lost to follow-up before age 2 (for reasons noted in ref. 20 only 318 of the 380 born into the study would have reached age 2 by December 1998) were compared with the 119 children included in this study. Those lost to follow-up actually had slightly lower birthweight (3139 g versus 3331 g, $P < 0.005$, independent sample t-test with unequal variances) and lower likelihood of water source in the home 48% versus 59%, $P < 0.05$, $\chi^2 = 4.60$). There were no significant differences in maternal education, family income, home size/quality, sanitary facilities or sanitary practices. Of the 119 with complete 0–2 year follow-up, 72 were age 7 by December 1998, and 31 of these 72 were still under nutritional surveillance at age 7. The 41 lost to follow-up actually had slightly lower mean HAZ and (weight-for-age) WAZ scores from ages 2–5 years. This was only statistically significant for WAZ at

age 3 (–1.22 versus –0.63, $P = 0.045$). They also had insignificantly more days of diarrhoea in their first 2 years of life (61 versus 41, $P = 0.102$). They did not differ in respect to maternal education, helminth recovery, home size/quality, water availability/sources, sanitary facilities/practices, family income, maternal education, or other variables included in the household questionnaires. Thus analysis of baseline data from dropouts illustrates that any selection bias would have biased us away from our conclusion that early childhood diarrhoea is associated with long-term linear growth retardation. Those lost to follow-up tended to have had lower birthweight and did less well nutritionally, thus any selection bias most likely would have biased us toward an underestimation of the true association of early childhood diarrhoea with later growth shortfalls.

There are several caveats to consider in interpreting these results. The first is the issue of diarrhoea and helminth infections after age 2 years. Although diarrhoea attack-rates in Gonçalves Dias drop considerably after age 2 years (from 6.8 to 4.1 episodes/child-year at 13–24 and 25–36 months old, respectively), children who have heavy diarrhoea burdens at age 0–2 years old have the most diarrhoea thereafter.²² The long-term inverse correlations we observed for early childhood diarrhoea and helminths versus nutritional status beyond age 2 years old might be a result of continued diarrhoea and helminth infections (or other malnourishing illnesses) in later childhood. *Ascaris* infections were treated, however, and a recent analysis of 26 cohort children ages 6–10 years old revealed only 4 children with *Ascaris* and 2 with *Trichuris*. Second, dropouts due to families moving from Gonçalves Dias were a limitation and a potential source of bias. The number of subjects in the older ages groups is a factor of both the number of children born in the project's early years and the number who remained under surveillance. Dropouts may have biased these results if factors in families' decisions to leave the project area were related to subjects' health (for which, however, we have no evidence). Finally, because helminth surveillance was not a primary focus of the Gonçalves Dias longitudinal surveillance project, our use of a dichotomous variable (*Ascaris* or *Trichuris* detected versus not detected during 0–2 years old) to classify children as exposed or unexposed may be an oversimplification.

World Health Organization efforts to target school-age children areas with a high prevalence of helminthiasis for mass chemotherapy-based treatments are well founded and will prove to be a highly cost-effective means of improving child health and cognitive function in these settings.³⁶ Our finding that helminthiasis in the first 2 years of life are associated with growth shortfalls suggests that extending mass treatment to preschool-age children, also a high risk group, may reap even greater benefits by preventing long-term growth deficits before they begin.

Would control of early childhood diarrhoea and helminths infections lead to lasting growth benefits? These data, although unable to assign a causal relationship between early childhood diarrhoea, helminths, and long-term growth faltering, strongly suggest so. Early childhood diarrhoea and helminths were highly significant predictors of growth shortfalls in later childhood, even when accounting for other possible covariates such as previous nutritional status and socioeconomic variables. In addition to the potential benefits to child growth, there is mounting evidence for other quality-of-life benefits to diarrhoea control

in early childhood. In this same cohort of children, we have found significant correlations of early childhood diarrhoea (and *Cryptosporidium* infections *per se*) with substantial decrements in physical fitness and cognitive function 4 to 7 years later that are independent of nutritional status growth shortfalls.⁶ Thus the potential clinical and public health significance of these statistically significant findings are substantial. If indeed confirmed and extended, these long-term effects at the critical developmental period in children would greatly amplify the importance and even potential economic value of key measures such as improved water, sanitation, and other measures to reduce early childhood diarrhoea and its potential long-term impact.

We conclude that early childhood diarrhoea and helminthiasis in the critical, formative first 2 years of life correlate, independently and additively, with substantial growth shortfalls. These growth shortfalls persist for 1 to 5 years later, into school age. Interventions targeting early childhood diarrhoea and helminthic infections in the first 2 years of life thus warrant further study and attention.

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