

# Catch-Up Growth Occurs after Diarrhea in Early Childhood<sup>1-3</sup>

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## Abstract

Diarrhea and linear growth faltering continue to burden low-income countries and are among the most important contributors to poor health during early childhood. Diarrhea is thought to adversely affect linear growth, but catch-up growth can occur if no additional insults are experienced. We sought to characterize catch-up growth in relation to diarrhea burden in a multisite dataset of 1007 children. Using longitudinal anthropometry and diarrheal surveillance data from 7 cohort studies in 4 countries, we examined the relation between diarrhea prevalence and growth in 3- to 6-mo periods using linear mixed-effect models. Growth during each period was calculated as a function of age using linear splines. We incorporated the longitudinal prevalence of diarrhea in both current and previous periods into the model. Diarrhea during the current period was associated with slower linear and ponderal growth. Faster (catch-up) growth in length was observed in children with no diarrhea in age groups immediately after an age group in which diarrhea was experienced [age group >6–12 mo: 0.03 mm/mo for each percentage diarrhea prevalence in the previous period (95% CI: 0.007, 0.06) relative to 11.3 mm/mo mean growth rate; age group >12–18 mo: 0.04 mm/mo (95% CI: 0.02, 0.06) relative to 8.9 mm/mo mean growth rate; age group >18–24 mo: 0.04 mm/mo (95% CI: 0.003, 0.09) relative to 7.9 mm/mo mean growth rate]. The associations were stronger in boys than in girls when separate models were run. Similar results were observed when weight was the outcome variable. When diarrheal episodes are followed by diarrhea-free periods in the first 2 y of life, catch-up growth is observed that may allow children to regain their original trajectories. The finding of a greater effect of diarrhea on linear growth in boys than in girls was unexpected and requires additional study. Diarrhea burdens are high throughout the first 2 y of life in these study sites, therefore reducing the likelihood of catch-up growth. Extending diarrhea-free periods may increase the likelihood of catch-up growth and decrease the prevalence of stunting. *J. Nutr.* 144: 965–971, 2014.

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## Introduction

Although improvements in child growth on a global scale have been observed over the past 20 y, 26% of children worldwide are stunted [height-for-age Z-score (HAZ) < -2] (1). Childhood stunting is indicative of inadequate dietary intake and high

infectious disease burdens and has been associated with both short-term (increased child mortality) and long-term (decreased educational attainment and economic productivity throughout adulthood) consequences (1). The association between diarrhea and linear growth during early childhood has been studied intensely in the literature, with some inconsistent findings (2–5). Many studies found a long-term association between overall diarrhea burden and height (5–15), although not all observed this association (16–19). Diarrhea represents a syndrome with a variety of etiologies and associated severity (20), and site-specific etiologies and treatment practices may modify the association, potentially resulting in inconsistent results.

Growth in early childhood is thought by some to be a saltatory process, alternating between periods of slower and faster growth (21). Among acutely malnourished children, it is thought that a child needs to recover in weight before resuming linear growth (22,23). Linear growth may falter if a child

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<sup>3</sup> Supplemental Text, Supplemental Figures 1 and 2, and Supplemental Tables 1–4 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://jn.nutrition.org>.

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experiences recurrent weight faltering associated with diarrhea episodes (3,24), but catch-up growth is possible given adequate diet and time between infections (25), as was demonstrated very successfully in international adoption studies (26). Nutritional supplementation was observed to offset the effect of diarrhea on growth faltering, likely through contributing to catch-up growth (8). However, the opportunity for catch-up growth may be missed if diarrhea-free periods are abbreviated, resulting in failure to achieve full biologic growth potential.

Previous studies primarily considered length (or HAZ) at a certain age as the outcome and summarized diarrhea burden over the entire period of follow-up. Although this method provides an estimate of the overall association between diarrhea and growth, it lacks precision with respect to timing and the potential for catch-up growth. A previous analysis performed using these data considered the lagged effects of diarrhea on growth over time and found that cumulative months with diarrhea had a small but significant effect on linear growth at age 2 y (5). Few studies have had the sample sizes available to quantify catch-up growth after a diarrheal episode. This study will consider the association between age-specific diarrhea burden and growth velocity in both length and weight, with the hypothesis that gaps between episodes of diarrhea allow for faster, catch-up growth to occur.

## Methods

**Study design.** We used growth and disease surveillance data from 7 cohort studies performed in four countries [Peru (11,13,27), Brazil (12), Guinea-Bissau (28,29), and Bangladesh (30)]. The studies are longitudinal cohorts that were conducted over a period of 2 decades and were performed in Africa, Asia, and Latin America (Supplemental Table 1). We searched for longitudinal cohort studies with diarrhea surveillance and anthropometry and obtained the original data whenever possible (31). Children were retained in the dataset if they had their first anthropometric measurement before age 2 mo and if they had at least 4 anthropometric measures before age 24 mo. We included 1007 children from 4 countries in this analysis (Table 1). Many of the studies collected anthropometry data on a monthly basis, whereas others collected anthropometry less frequently. HAZ and weight-for-age Z-score (WAZ) were calculated using the WHO Multicenter Growth Reference Study program (32). At baseline, 14% of the children were stunted, whereas at the final anthropometric measure (ages 12–24 mo), 37% of the children were stunted (Table 1).

Field workers visited families at least twice a week to collect daily diarrhea data in all of the studies except for Guinea-Bissau, which collected daily diarrhea data on a weekly basis. The definition of

diarrhea for the studies was  $\geq 3$  liquid or semiliquid stools in a 24-h period, and diarrhea episodes were separated by 2 diarrhea-free days. Mean diarrhea prevalence ranged from 9 d/y in Peru 1995 to 44 d/y in Guinea-Bissau 1987. Diarrhea burden was similar in girls and boys in most of the studies (Table 1). The majority of diarrhea episodes were acute (duration: <8 d), 12% were prolonged (duration: 8–14 d), and 4% were persistent (duration: >14 d) (Table 1).

**Biostatistical methods.** To quantify the association between diarrhea and linear and ponderal (weight) growth velocity, we modeled growth as a piecewise linear function of age with knots at 3, 6, 12, and 18 mo (Figs. 1 and 2). Also included in the model is a coefficient for sex, indicator variables for each study, and whether the child was moderately underweight (WAZ < -1) at their first visit, which occurred before age 2 mo. We accounted for heterogeneity in growth among children using random effects for the intercept ( $b_0$ ) and age ( $b_1$ ) by child. Diarrhea burden was added to the model as an interaction term with age for each of the current and previous time periods. Model details can be found in the Supplemental Text. Lengths and weights at age 24 mo were estimated using 3 categories of diarrhea burden: 0%, the mean percentage diarrhea burden in each time period (5%, 7%, 8%, 7%, and 5% in the age groups 0–3, >3–6, >6–12, >12–18, and >18–24 mo), and twice the mean percentage diarrhea burden in each period (10%, 14%, 16%, 14%, and 10% diarrhea prevalence in the age groups 0–3, >3–6, >6–12, >12–18, and >18–24 mo). Wald tests were used to test for interactions between age, diarrhea burden, and sex. We used R version 2.14.2 (33) for statistical analyses, specifically, the nlme package for the random-effects models, the gmodels package to derive the predicted effects at age 24 mo, and the graphics package for the figures.

## Results

**Association between diarrhea and linear growth.** In Figure 3, we display the percentage of days ill with diarrhea in children by age group. Specifically, we show that diarrhea burden was greatest between 6 and 18 mo and that there appeared to be little difference in diarrhea burden with sex. We calculated the association between diarrhea and linear growth during each period, overall and by sex (Supplemental Table 2). Diarrhea during the current period was associated with lower length velocity during all time periods (Fig. 4A). When stratified by sex, the confidence interval for the association between concurrent diarrhea and length velocity did not overlap 0 in boys at >3–6, >6–12, and >18–24 mo. Although all of the point estimates for girls were negative, all of the confidence intervals overlapped 0.

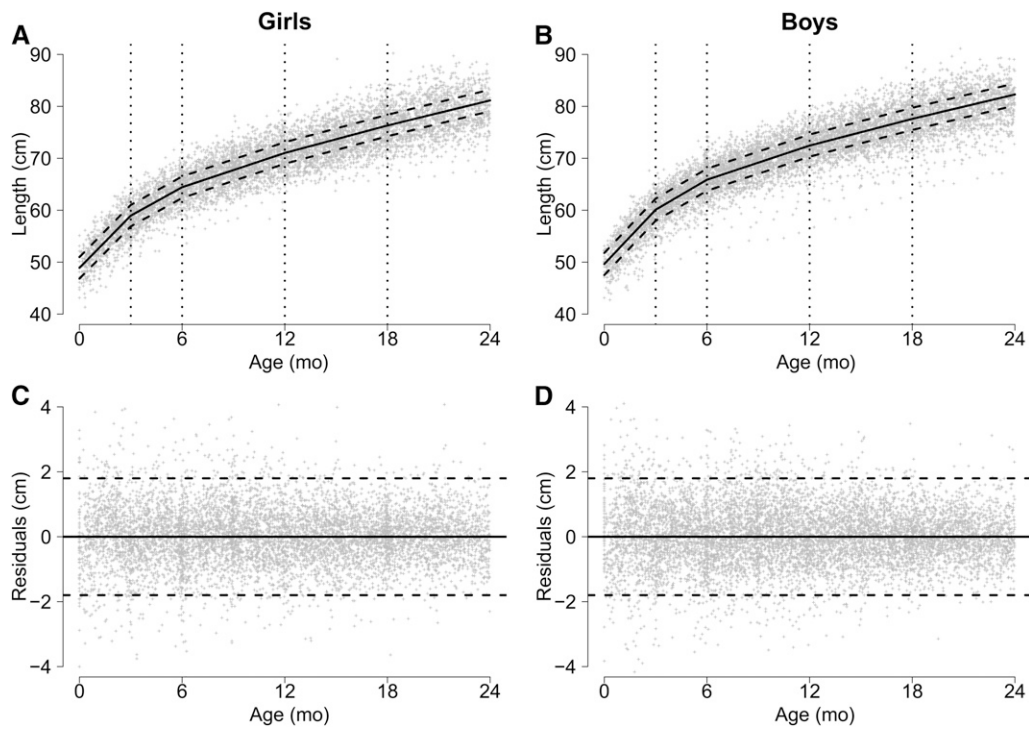
Interaction terms considering age, diarrhea burden, and sex were important (age  $\times$  sex interaction,  $P < 0.001$ ; 3-way interaction of age  $\times$  diarrhea  $\times$  sex,  $P = 0.01$ ); therefore, we

**TABLE 1** Description of studies included in the combined dataset<sup>1</sup>

Location, year	Reference	Participants	Male	Mean length measures	Stunted (HAZ < -2)		Mean diarrhea prevalence per year <sup>2</sup>			Acute episodes	Prolonged episodes	Persistent episodes
					Baseline	Final	Overall	Girls	Boys			
		<i>n</i>	<i>n</i> (%)	<i>n</i>		%	<i>d/y</i>	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Peru, 1985	Lanata et al. (27)	111	56 (50)	19	5	32	33	33	32	1289 (89)	124 (9)	34 (2)
Peru, 1989	Checkley et al. (11)	83	44 (53)	17	1	19	32	34	30	384 (74)	72 (14)	60 (12)
Peru, 1995	Checkley et al. (13)	157	87 (55)	20	5	25	9	9	9	894 (96)	31 (3)	2 (0.2)
Brazil, 1989	Moore et al. (12)	118	56 (47)	7	4	23	23	22	25	788 (81)	126 (13)	55 (6)
Guinea-Bissau, 1987	Mølbak et al. (28)	79	37 (47)	6	9	41	44	38	50	910 (84)	124 (11)	47 (4)
Guinea-Bissau, 1996	Valentiner-Branth et al. (29)	209	96 (46)	10	10	23	24	22	26	1564 (87)	177 (10)	55 (3)
Bangladesh, 1993	Pathela et al. (30)	250	142 (57)	21	38	69	24	23	25	1507 (76)	393 (20)	82 (4)
Total		1007	518 (51)	15	14	37	25	24	25	7336 (84)	1047 (12)	335 (4)

<sup>1</sup> HAZ, height-for-age Z-score.

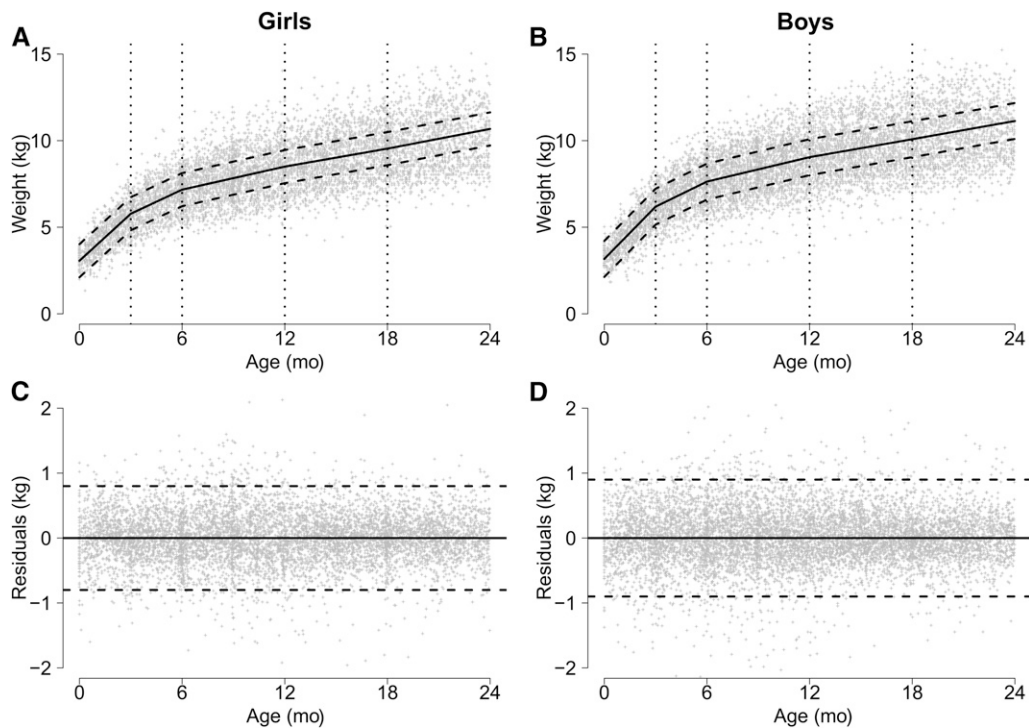
<sup>2</sup> Mean diarrhea prevalence =  $n$  diarrhea days/ $n$  surveillance days  $\times$  365.



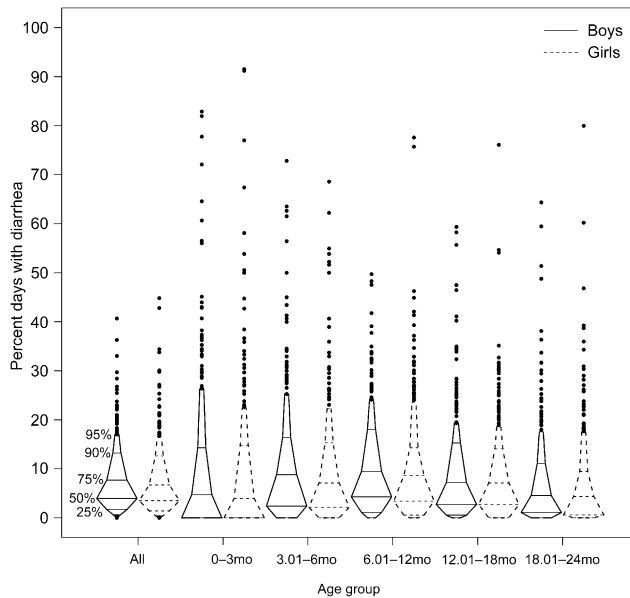
**FIGURE 1** Relation between age and length (A, B) and residuals (C, D), by sex, in a combined dataset including anthropometry data collected in children aged <24 mo from 7 cohort studies. Spline model (solid line) has knots at ages 3, 6, 12, and 18 mo. The dashed lines represent  $\pm 2$  SDs.

present the sex-specific analyses and the overall model results in some cases for comparison. Individual Wald tests were important only for the interactions age  $\times$  sex in the age groups 0–3 mo ( $P = 0.02$ ) and >6–12 mo ( $P = 0.01$ ) and age  $\times$  diarrhea  $\times$  sex during the age group >6–12 mo ( $P = 0.04$ ).

**Catch-up linear growth.** Catch-up growth in the absence of current diarrhea was indicated by the positive coefficients associated with diarrhea during the previous period (Supplemental Fig. 1). If the child did not have additional diarrhea during the current period, linear growth would speed up, potentially returning the child to his



**FIGURE 2** Relation between age and weight (A, B) and residuals (C, D), by sex, in a combined dataset including anthropometry data collected in children aged <24 mo from 7 cohort studies. Spline model (solid line) has knots at ages 3, 6, 12, and 18 mo. The dashed lines represent  $\pm 2$  SDs.



**FIGURE 3** Percentage of days with diarrhea overall and during 3- to 6-mo time periods, by sex.

or her original trajectory, and this trend toward catch-up growth was observed in all age groups (Fig. 4B). Diarrhea in the previous time period followed by no diarrhea in the current time period was associated with higher length velocity overall, with some minor differences by sex.

**Length at age 24 mo.** We can estimate the length of children at age 24 mo based on the model results according to different diarrhea scenarios. No diarrhea during the first 2 y of life was associated with greater length at age 2 y when compared with the mean or twice the mean diarrhea prevalence (Fig. 5A; Supplemental Table 3). This association appeared to be stronger in boys than in girls when the models are run separately (Fig. 5B, C; Table 2). Considering the sex-specific model estimates, the cumulative association between the mean diarrhea prevalence and length at age 24 mo was equivalent to 0.7-cm shorter length in boys ( $HAZ = -0.2$ ) at age 24 mo compared with children with no diarrhea. Twice the mean burden of diarrhea was associated with 1.4-cm shorter length in boys ( $HAZ = -0.4$ ) at age 24 mo. No relation between diarrhea and linear growth was observed in girls. Subgroup analysis by study demonstrates qualitatively similar but not statistically significant results in most studies (Supplemental Fig. 2).

**Association between diarrhea and weight gain.** We observed similar trends with models using weight as the primary outcome (Supplemental Table 4). Diarrhea during the current period was negatively associated with weight gain in most age groups, and associations were somewhat similar for boys and girls (Fig. 6A). Boys lost more weight than girls did, on average, as a result of diarrhea in the age group >3–6 mo.

**Catch-up ponderal growth.** Catch-up ponderal growth was found in the overall model and ranged from 1 to 4 g/mo per percentage diarrhea prevalence in the previous age group (Fig. 6B). The confidence intervals for catch-up ponderal growth did not overlap 0 in boys in the age groups >6–12, >12–18, and >18–24 mo and for girls in the age group >12–18 mo.

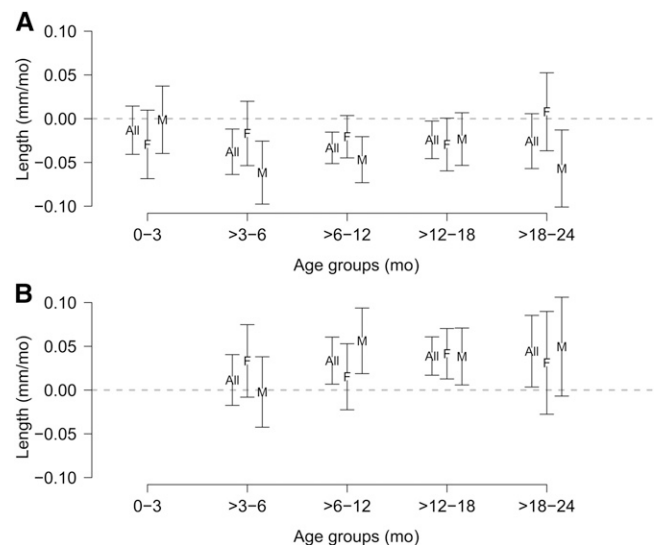
**Weight at age 24 mo.** No diarrhea in the first 2 y of life was associated with greater weight when compared with the mean

diarrhea burden (Fig. 5D), and, as with length, this relation appeared to be greater in boys (Fig. 5E, F; Table 2). Overall, mean diarrhea burden was associated with 0.1 lower WAZ compared with children with no diarrhea (Supplemental Table 3). Mean diarrhea prevalence was associated with 0.2-kg lower weight in boys ( $WAZ = -0.2$ ), and twice the mean diarrhea prevalence was associated with 0.3-kg lower weight in boys ( $WAZ = -0.3$ ) (Table 2). No association between diarrhea and ponderal growth was observed in girls.

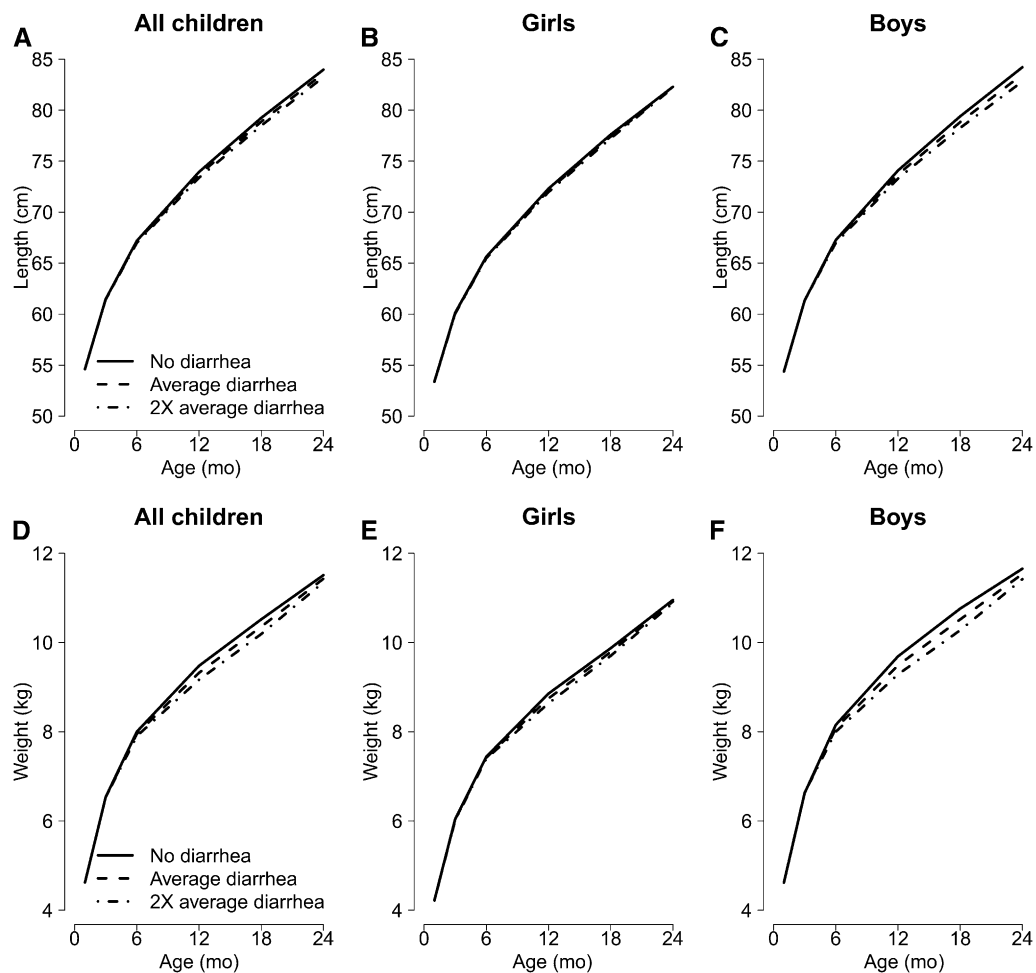
## Discussion

Diarrhea was associated with decreased linear and ponderal growth in early childhood, but catch-up growth was observed if diarrhea prevalence decreased from one period to the next. Persistent growth deficits may be associated with repeated diarrheal insults that serve to prevent catch-up growth in the first 2 y of life. Subgroup analysis indicates that boys may experience more linear growth faltering after diarrhea than girls do, but more research is needed to explore these findings.

Catch-up growth has been documented in a number of previous studies. Catch-up growth in weight was documented by Ashworth (22) who demonstrated increased rates of weight acquisition in severely malnourished children who consumed food ad libitum and catch-up growth in length was observed in subgroups of children at a feeding center in the West Indies (34). Nutritional supplementation was found to either decrease growth faltering after diarrhea or increase chances of catch-up growth in length to occur, therefore eliminating the effect of diarrhea on linear growth in a study in Colombia (8). The results from this study in which some children were administered a protein-rich nutritional supplementation vs. none suggests the importance of diet in reducing the risk of growth faltering or increasing the chance of catch-up growth after diarrhea. In a study in Egypt, the relation between diarrhea and growth was decreased when there was sufficient time (3–6 mo) since the last



**FIGURE 4** Difference in length slopes at 0–3, >3–6, >6–12, >12–18, and >18–24 mo contributed by current period diarrhea prevalence (A) and previous period diarrhea prevalence (B), overall and by sex. Values are coefficients produced by the models and represent difference in slope measured in millimeters per month of age associated with percentage of days with diarrhea during that period (A) or the previous period (B). All, overall; F, female; M, male.



**FIGURE 5** Growth trajectories (length in A–C, weight in D–F) of children with different burdens of diarrhea [no diarrhea, the mean burden of diarrhea (5%, 7%, 8%, 7%, and 5% of days with diarrhea in the age groups 0–3, >3–6, >6–12, >12–18, and >18–24 mo, respectively), and twice the mean burden of diarrhea during the first 2 y of life], overall and by sex, from a combined dataset including data from 7 cohort studies.

diarrhea had occurred, allowing for catch-up growth (17). Similarly, children in Brazil with high diarrhea prevalence during multiple periods were found to grow less than children without recurrent high amounts of diarrhea (3). Finally, catch-up growth was observed in a study that considered the effect of *Cryptosporidium parvum* on linear growth faltering, but the extent of catch-up growth differed depending on the age of infection and presence of malnutrition at baseline, with some age groups recovering fully and others experiencing persistent deficits (11,24). The model we used allowed us to observe catch-up growth in the absence of diarrhea, and we quantified the negative association between repeated diarrheal episodes and

catch-up growth during the first 2 y of life. Simpler models that consider only the relation between overall diarrhea burden and growth may miss the more nuanced relation described here. In addition, summary models will be less likely to observe an association between diarrhea and growth, because the timing of episodes will affect the relation with growth faltering.

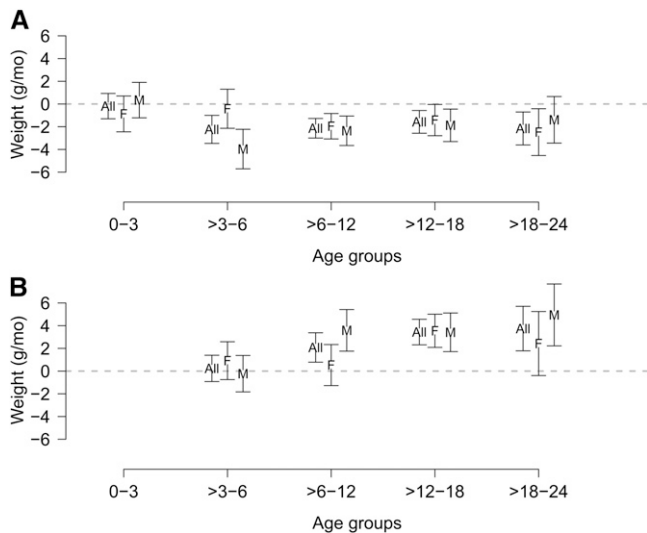
The suggestion of differential associations between diarrhea prevalence and growth by sex may be partially due to somewhat lower diarrhea burdens in girls than in boys. Another possible biologic mechanism for differential association between diarrhea and linear growth by sex has to do with zinc deficiency, which is associated with growth faltering, poor immune

**TABLE 2** Estimates of length, HAZ, weight, and WAZ at age 24 mo<sup>1</sup>

Diarrhea burden	Boys				Girls			
	Length	HAZ	Weight	WAZ	Length	HAZ	Weight	WAZ
	<i>cm</i>		<i>kg</i>		<i>cm</i>		<i>kg</i>	
No diarrhea	84.2 (83.7, 84.7)	-1.0 (-1.1, -0.8)	11.7 (11.5, 11.9)	-0.3 (-0.5, -0.2)	82.3 (81.8, 82.8)	-1.1 (-1.2, -0.9)	11.0 (10.8, 11.2)	-0.4 (-0.5, -0.2)
Mean burden <sup>2</sup>	83.5 (83.0, 84.0)	-1.2 (-1.4, -1.0)	11.5 (11.3, 11.7)	-0.5 (-0.6, -0.3)	82.2 (81.7, 82.7)	-1.1 (-1.3, -0.9)	10.9 (10.7, 11.1)	-0.4 (-0.6, -0.3)
2× Mean burden	82.8 (82.2, 83.4)	-1.4 (-1.6, -1.2)	11.4 (11.2, 11.6)	-0.6 (-0.7, -0.4)	82.2 (81.7, 82.7)	-1.1 (-1.3, -0.9)	10.9 (10.7, 11.1)	-0.4 (-0.6, -0.3)

<sup>1</sup> Data are presented as estimates (95% CIs). The models were run separately for boys and girls. HAZ, height-for-age Z-score; WAZ, weight-for-age Z-score.

<sup>2</sup> The mean burden of diarrhea overall is 5%, 7%, 8%, 7%, and 5% of days with diarrhea in the age groups 0–3, >3–6, >6–12, >12–18, and >18–24 mo, respectively.



**FIGURE 6** Difference in weight slopes at 0–3, >3–6, >6–12, >12–18, and >18–24 mo contributed by current period diarrhoea prevalence (A) and previous period diarrhoea prevalence (B), overall and by sex. Values are coefficients produced by the models, which represent difference in slope measured in grams per month of age associated with percentage of days with diarrhoea during that period (A) or the previous period (B). All, overall; F, female; M, male.

function, and increased incidence and severity of diarrhoea, and is thought to be widespread in developing countries (1). In general, boys are at greater risk of zinc deficiency than girls (35). Zinc can be lost during diarrhoea; therefore, if diarrhoea burden is higher in boys, they will be at greater risk of zinc deficiency. Another potential contributing factor may be different underlying biologic responses to diarrhoea in boys and girls, which is supported by a similar finding in research into the effect of inflammatory bowel diseases and Crohn disease on growth (36–39). Girls were found to have more severe symptoms of Crohn disease than boys; however, boys were more likely to develop growth failure than girls (38) and were observed to have impaired catch-up growth when compared with girls (36).

There are a number of unmeasured variables that potentially play a role in these overall and sex-specific relations, including etiology of infection, treatment factors, socioeconomic status, and feeding practices, among others; these variables were not available in the combined dataset used for this analysis. The use of multiple cohorts in a combined analysis allowed for a more detailed analysis than has been implemented previously by single-cohort studies, but our findings highlight the need for a comprehensive, standardized multicenter study similar to the MAL-ED (The Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development) cohort (40). In an initial publication about the MAL-ED cohort, measures of intestinal inflammation were associated with linear growth faltering, even after controlling for overt diarrhoeal illness (40). This finding supports previous assertions that tropical enteropathy, resulting from exposure to enteric pathogens and characterized by impairment of the absorptive and barrier functions of the gut (41), is an undervalued contributor to stunting. Considering the conceptual framework of Humphrey (41), high amounts of exposure to enteric pathogens results in tropical enteropathy, which plays a large role in growth faltering, even in the absence of overt diarrhoea. Water and sanitation activities could have large impacts on stunting prevalence through decreasing the burden

of enteric infection (41,42). Future work in this area should include additional exploration of the relation between enteric infection (with or without diarrhoea, as identified by fecal markers of infection or pathogen identification) and linear growth, as well as additional variables, such as diet, etiology, treatment, and socioeconomic status.

In addition to finding a negative association between diarrhoea and linear growth velocity in early childhood, we were able to quantify the faster, catch-up growth that occurred in subsequent diarrhoea-free periods (Fig. 4). Unfortunately, in many low-resource settings, diarrhoea and other infectious insults in conjunction with nutritional deficiencies are ubiquitous, and catch-up growth does not occur. Long-term linear growth faltering can result from these continued insults during childhood; therefore, prevention of diarrhoea and extension of diarrhoea-free periods in early childhood may improve linear growth. The suggestion of a greater detrimental effect of diarrhoea on growth in boys than girls is somewhat novel and requires additional study. Decreasing the burden of diarrhoea in populations will also decrease mortality associated with diarrhoea in the population; therefore, diarrhoea prevention programs (e.g., rotavirus vaccine, breastfeeding, zinc supplementation, and improved water and sanitation) should be prioritized to improve child health.

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