Diarrhea in Early Childhood: Short-term Association With Weight and Long-term Association With Length


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The short-term association between diarrhea and weight is well-accepted, but the long-term association between diarrhea and growth is less clear. Using data from 7 cohort studies (Peru, 1985–1987; Peru, 1989–1991; Peru, 1995–1998; Brazil, 1989–1998; Guinea-Bissau, 1987–1990; Guinea-Bissau, 1996–1997; and Bangladesh, 1993–1996), we evaluated the lagged relationship between diarrhea and growth in the first 2 years of life. Our analysis included 1,007 children with 597,638 child-days of diarrhea surveillance and 15,629 anthropometric measurements. We calculated the associations between varying diarrhea burdens during lagged 30-day periods and length at 24 months of age. The cumulative association between the average diarrhea burden and length at age 24 months was −0.38 cm (95% confidence interval: −0.59, −0.17). Diarrhea during the 30 days prior to anthropometric measurement was consistently associated with lower weight at most ages, but there was little indication of a short-term association with length. Diarrhea was associated with a small but measurable decrease in linear growth over the long term. These findings support a focus on prevention of diarrhea as part of an overall public health strategy for improving child health and nutrition; however, more research is needed to explore catch-up growth and potential confounders.

child health; diarrhea; malnutrition; stunting; wasting

Abbreviations: LAZ, length-for-age z score; SES, socioeconomic status; WHO, World Health Organization; WLZ, weight-for-length z score.

Diarrhea is a manifestation of intestinal infection with a variety of different bacteria, parasites, or viruses, and it is common in low-income countries where water and sanitation facilities are inadequate (1). Diarrhea has consistently been associated with decreased weight over the short term (2–10), but the longer-term impact of diarrhea on weight has been less consistently documented and is more controversial (11, 12). Some studies have identified a long-term association between diarrhea and ponderal growth (8, 10, 13–16), whereas others have not (5, 7, 17). The relationship between diarrhea and both short- and long-term linear growth is similarly mixed across studies (2, 4–10, 13–15, 17–26), perhaps demonstrating the potential for catch-up growth in children, provided that they have adequate nutritional resources and time between diarrhea episodes. Other factors that may contribute to inconsistent results include socioeconomic status (SES), dietary quality, access to health care, breastfeeding practices, and diarrhea etiology, as well as differences in study design and implementation.

Although catch-up linear growth is possible (27–30), small size at birth, frequent enteric infections, and inadequate diet are thought to result in linear growth retardation from which recovery may not be possible (28). The mechanisms by which enteric infections are thought to lead to impaired linear and ponderal growth include reduced dietary intake, increased metabolic demands, and decreased gut function/nutrient absorption.
Children with enteric infections may consume less food, lower-quality food, or both; and the nutrients that are consumed may be poorly absorbed, due either to damaged intestinal epithelium or mucosa or to bacterial overgrowth that may persist long after the acute diarrhea episode has resolved (32). Weight may be lost during the course of infection; during recovery, linear growth may slow down until weight is regained (29). Linear growth faltering is associated with decreased educational attainment, work capacity, and economic potential in adulthood, as well as increased risk of chronic diseases (33). Weight faltering is thought to be temporary and has been associated with increased mortality (34).

Using data from 7 cohort studies, we evaluated the short- and long-term relationships between diarrhea and weight and length in children under 2 years of age. Our study augmented the extensive existing research on this topic through the use of both traditional methods of combining data from multiple cohorts and novel methods that allow more detailed analysis. In a similar analysis, Checkley et al. (35) found that the overall diarrhea burden was associated with greater odds of stunting at 24 months of age; however, this previous analysis was unable to distinguish whether this association reflected a direct adverse effect of diarrhea on linear growth or was due to reverse causality. In this article, we take a more nuanced approach to model the short- and long-term relationships between diarrhea burden and weight and length at different ages, while allowing for potential catch-up growth.

**Materials and Methods**

**Study design**

We combined data from 7 longitudinal cohort studies carried out in 4 countries (Peru, 1985–1987 (36); Peru, 1989–1991 (17); Peru, 1995–1998 (18); Brazil, 1989–1998 (23); Guinea-Bissau, 1987–1990 (37); Guinea-Bissau, 1996–1997 (38); and Bangladesh, 1993–1996 (39)); details on our search methods have been published previously (35). Briefly, we searched in a variety of sources for longitudinal studies with data on diarrhea and anthropometric measures in early childhood and obtained the original data from the authors, whenever possible. One cohort has been added since the original work was published (39). Three of the studies that were included originally were excluded from our current analysis because we used more stringent eligibility criteria (described below) for this analysis.

**Eligibility criteria**

We limited our analysis to children under 24 months of age. We excluded unusual length measurements (>2.5-cm change in length in comparison with both surrounding measurements). We then applied our eligibility criteria, which included enrollment at less than 3 months of age, relatively complete diarrhea data for at least 1 year (no gaps greater than 60 days), and at least 4 anthropometric measurements. Length-for-age z score (LAZ) and weight-for-length z score (WLZ) were calculated using the World Health Organization (WHO) Multicentre Growth Reference Study program (40).

<table>
<thead>
<tr>
<th>First Author, Year of Study</th>
<th>Location of Study</th>
<th>Dates of Study</th>
<th>No. of Children</th>
<th>Male Gender</th>
<th>Type of Diarrhea</th>
<th>Incidence (Mean No. of Days of Diarrhea per Year)</th>
<th>Prevalence (Mean No. of Days of Diarrhea per Year)</th>
<th>No. of Height Measurements</th>
<th>Sacramento Area</th>
<th>Los Angeles</th>
<th>Bissau</th>
<th>Pinnibulg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richard et al., 2013</td>
<td>Peru</td>
<td>1985–1987</td>
<td>126</td>
<td>62%</td>
<td>Acute</td>
<td>3.44</td>
<td>3.04</td>
<td>4</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1.07</td>
</tr>
<tr>
<td>et al.</td>
<td></td>
<td>1989–1991</td>
<td>108</td>
<td>64%</td>
<td>Prolonged</td>
<td>1.72</td>
<td>2.72</td>
<td>1</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>0.34</td>
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<td></td>
<td></td>
<td>1995–1998</td>
<td>115</td>
<td>75%</td>
<td>Persistent</td>
<td>1.78</td>
<td>2.78</td>
<td>1</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>0.34</td>
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<td>1987–1990</td>
<td>143</td>
<td>90%</td>
<td></td>
<td>1.76</td>
<td>2.76</td>
<td>1</td>
<td>1/3</td>
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<td>1/3</td>
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<td>1996–1997</td>
<td>242</td>
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<td></td>
<td>1.89</td>
<td>2.89</td>
<td>1</td>
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<td>1/3</td>
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<td>1998–1999</td>
<td>196</td>
<td>13%</td>
<td></td>
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<td>2.95</td>
<td>1</td>
<td>1/3</td>
<td>1/3</td>
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<td>1/3</td>
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</tr>
<tr>
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<td></td>
<td>1,007</td>
<td>53%</td>
<td></td>
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<td>1.07</td>
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<td>1/3</td>
<td>1/3</td>
<td>1/3</td>
<td>1.07</td>
</tr>
</tbody>
</table>

a Mean diarrhea prevalence was calculated as the ratio of the number of surveillance days to the number of diarrhea episodes × 365.

b Mean diarrhea incidence was calculated as the ratio of the number of new diarrhea episodes to the number of surveillance days × 365.

c Diarrhea included in the first day of the episode; prolonged: ≥15 days in duration; acute: <7 days in duration; transitional: 7–14 days in duration.
Definitions

We used the study-specific definitions of diarrhea, all of which specified at least 3 or more loose stools within a 24-hour period. We separated diarrhea episodes by at least 2 diarrhea-free days. All days within an episode were considered to be days with diarrhea. Diarrhea prevalence was calculated as the ratio of diarrhea days to the number of days under surveillance. Diarrhea incidence was calculated as the ratio of the number of new episodes to the number of days at risk for a diarrheal episode. Stunting was defined as LAZ < -2, and wasting was defined as WLZ < -2.

Figure 1. Length (cm) and weight (kg) measurements from birth to age 23.9 months in an analysis of the association of diarrhea with weight and length, by gender (parts A and C, boys (left); parts B and D, girls (right)), among children from a multisite data set (Peru, 1985–1987 (36); Peru, 1989–1991 (17); Peru, 1995–1998 (18); Brazil, 1989–1998 (23); Guinea-Bissau, 1987–1990 (37); Guinea-Bissau, 1996–1997 (38); and Bangladesh, 1993–1996 (39)). For comparison, dotted lines indicating the World Health Organization median and dashed lines indicating ±2 z scores are superimposed on the data.

Figure 2. Mean weight-for-length z score (WLZ) (A) and length-for-age z score (LAZ) (B) from birth to age 23.9 months, by study, among children from a multisite data set (Peru, 1985–1987 (36); Peru, 1989–1991 (17); Peru, 1995–1998 (18); Brazil, 1989–1998 (23); Guinea-Bissau, 1987–1990 (37); Guinea-Bissau, 1996–1997 (38); and Bangladesh, 1993–1996 (39)). Lines were generated using a smoothing spline through the mean values at each month of age.
Biostatistical methods

The primary objective of our study was to quantify the relationship between diarrhea and length and weight in early childhood. We used smoothing splines to represent the trajectories of mean monthly WLZ, LAZ, diarrhea prevalence, and diarrhea incidence during the first 24 months of life in each of the studies. We used linear regression to quantify the study-specific relationship between LAZ at 24 months of age and diarrhea prevalence, sex, and baseline LAZ (first measurement between birth and 3 months of age).

We explored 4-month length and weight velocity in a subset of children between 6 and 24 months of age. Weight and length differences when measurements were between 90 and 150 days were calculated and standardized, and the prevalence of diarrhea in each half of the period was calculated. We used mixed-effects models to calculate the study-specific relationship between diarrhea prevalence in the first and second halves of the 4-month period, interaction between prevalence in both periods, gender, and LAZ at the beginning of the period and length and weight velocity, with random effects for child.

We used mixed-effects models to quantify the lagged relationship between diarrhea in previous months and weight and length at each month of age. We calculated the number of days with diarrhea in lagged 30-day periods prior to each anthropometric measurement. Age was included in the model as a natural cubic spline, with knots at 1.5, 3, 6, 12, and 18 months of age. Fixed effects in the model included dummy variables for study, sex, 6 natural cubic spline terms, and interactions between 24 monthly diarrhea lags and 24 months of age. Since we had multiple measurements per child and 7 different studies, a random effect for age and child was included, and the standard errors were adjusted for the study grouping. In addition, we included a first-order continuous autoregressive error function that accounted for correlation by age, within-child. Assuming that the lagged diarrhea estimates were additive, we estimated the cumulative effect of having the average burden of diarrhea

Figure 3. Mean prevalence of diarrhea (number of days with diarrhea per year) (A) and incidence of diarrhea (number of diarrhea episodes per year) (B) from birth to age 23.9 months, by study, among children from a multisite data set (Peru, 1985–1987 (36); Peru, 1989–1991 (17); Peru, 1995–1998 (18); Brazil, 1989–1998 (23); Guinea-Bissau, 1987–1990 (37); Guinea-Bissau, 1996–1997 (38); and Bangladesh, 1993–1996 (39)). Lines were generated using a smoothing spline through the mean values at each month of age.

Figure 4. Difference in length-for-age z score (LAZ) at age 24 months per day of diarrhea experienced during follow-up, overall and by study, among children from a multisite data set (Peru, 1985–1987 (36); Peru, 1989–1991 (17); Peru, 1995–1998 (18); Brazil, 1989–1998 (23); Guinea-Bissau, 1987–1990 (37); Guinea-Bissau, 1996–1997 (38); and Bangladesh, 1993–1996 (39)). Estimates were produced using a regression model with LAZ as the dependent variable and gender, diarrhea prevalence, and baseline LAZ as the independent variables. The size of the rectangle is proportional to the weight (1/SE^2) of the study, and the 95% confidence interval is indicated by the width of the line. The width of the diamond indicates the 95% confidence interval for the pooled fixed estimate. SE, standard error.
at all months of age, half the average burden, and 4 times the average burden. We also considered the situation in which the average diarrhea burden was experienced during the first 6 months of life and then no diarrhea was experienced and, conversely, the situation in which no diarrhea was experienced during the first 6 months of life and then the average diarrhea burden was experienced.

We conducted data management in Stata, version 12.1 (StataCorp LP, College Station, Texas), and analysis in R, version 2.14.0 (www.r-project.org), and SAS, version 9.1.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Growth data

A total of 1,007 children were included in the final combined data set, contributing 15,629 length and weight...
measurements (Table 1). On average, the children began life at or slightly below the WHO Multicentre Growth Reference Study median for both weight and length. Thereafter, gender-specific distributions of weight and length were increasingly lower than the WHO Multicentre Growth Reference Study median (Figure 1).

**Longitudinal trends in reference-adjusted growth measurements (WLZ and LAZ)**

The study-specific mean WLZ at the beginning of follow-up ranged from –0.6 to 0.7. The mean WLZ increased during the first 24 months of life in most of the studies, although the mean WLZ decreased somewhat in the Guinea-Bissau 1996–1997 (39) and Bangladesh 1993–1996 (40) studies (Figure 2A). Mean LAZ decreased sharply with increasing age in all of the studies (Figure 2B). Bangladesh 1993–1996 (40) had the lowest mean LAZ at both the beginning (–1.8) and end (–2.6) of follow-up.

**Longitudinal prevalence and incidence of diarrhea**

Mean diarrhea burden in the studies ranged from 8.9 to 47.3 diarrhea days per child-year, and mean diarrhea incidence ranged from 3.5 to 10.4 diarrhea episodes per child-year (Table 1). Most diarrhea episodes lasted for ≤7 days (84%). Mean diarrhea burden varied both across the studies and across age groups within-study (Figure 3A), with a peak burden observed for many of the studies at approximately 6–12 months of age. Similar patterns were observed for diarrhea incidence (Figure 3B). It is unclear whether the high diarrhea burden during the first month of life in the Peru 1989–1991 study (17) was real or a result of misclassification of normal newborn loose stools as diarrhea. Over half of the 78 children in the Peru 1989–1991 study (17) did not have any diarrhea, but 9 children had more than 20 days of reported diarrhea in the first month of life.

**Overall association of longitudinal diarrhea prevalence with LAZ at 24 months**

Initially, we explored the relationship between overall longitudinal diarrhea prevalence and LAZ at 24 months of age (Figure 4). Overall, every 10 additional days of diarrhea per child-year of follow-up had a negative relationship with LAZ at 24 months of age (change in LAZ: –0.1, 95% confidence interval: –0.1, –0.0; P = 0.000).

**Association between cumulative diarrhea burden and weight/length velocity**

Little association with weight velocity was observed when diarrhea was experienced only during the first half of the 4-month period (Figure 5A), whereas diarrhea during the second half of the period was negatively associated with weight velocity (Figure 5B). The number of days with diarrhea in the first half of the 4-month period was negatively associated with length velocity only in the Peru 1985–1987 (36) and Guinea-Bissau 1996–1997 (38) studies (Figure 6A). Diarrhea in the second half of the period was also negatively associated with length velocity in the Guinea-Bissau 1996–1997 study (38) (Figure 6B).

**Relationship between diarrhea in lagged 30-day periods and weight and length at 18 months**

Using the estimates from the lagged 30-day model at 18 months as an example, children who had experienced diarrhea in the past 30 days weighed less than children who had had no diarrhea in the past 30 days (Figure 7A). Several other lags were associated with lower weight at age 18 months (5-, 10-, and 16-month lags). There was no statistically significant association between diarrhea during any single lagged period and length at 18 months of age (Figure 7B), except for the lagged 6-month period (corresponding loosely to the 12th month of life).

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Figure 7. Difference in weight (A) and length (B) associated with 1 day of diarrhea in lagged 30-day periods among 18-month-old children from a multisite data set (Peru, 1985–1987 (36); Peru, 1989–1991 (17); Peru, 1995–1998 (18); Brazil, 1989–1998 (23); Guinea-Bissau, 1987–1990 (37); Guinea-Bissau, 1996–1997 (38); and Bangladesh, 1993–1996 (39)). Estimates were generated using mixed-effects models with fixed effects for study, a natural cubic spline for age with 5 knots, gender, and diarrhea prevalence in lagged 30-day periods for each month of age. Random effects for child, grouped by study, were included in the model, as well as a first-order continuous autoregressive error function that accounted for correlation by age within-child. Point estimates and 95% confidence intervals (vertical lines) are shown.
Using the lagged model results, we extracted the age-specific weight estimates associated with diarrhea in the 1- to 30-, 31- to 60-, and 61- to 90-day periods prior to measurement to see whether the age at which diarrhea occurred modified the short-term association between diarrhea and weight (Figure 8).

Diarrhea during the past 30 days was associated with lower weight at most ages, although the associations were not significant in some of the younger (1, 2, 3, and 5 months) and older (20, 22, and 23 months) age groups. Diarrhea during 2- and 3-month lagged periods was not as strongly associated with weight as in the 1-month lagged periods. There were few statistically significant relationships between diarrhea in the 1-, 2-, or 3-month lagged periods and length at any age (Figure 8).

Cumulative association between diarrhea and length

We estimated the associations between different levels of diarrheal illness and length at 24 months of age (Figure 9) using the estimates from the lagged model. A child with the average age-specific monthly diarrhea burden (equivalent to 23 diarrhea days per year) was 0.38 cm shorter at age 24 months than a child with no diarrhea. Finally, we considered different scenarios involving the first 6 months of life. A child with no diarrhea during the first 6 months of life who then experienced the average diarrhea burden from age 7 months to age 24 months was 0.24 cm shorter than a child without diarrhea. Conversely, a child with the average diarrhea burden during the first 6 months of life who then went on to have no diarrhea was not statistically significantly shorter than a child with no diarrhea, which demonstrates the potential for catch-up growth. The average length for boys in the Peru 1985–1987 study (36) was 82.98 cm with no diarrhea and 82.59 cm with the average burden of diarrhea. To compare these average lengths with the WHO growth expectation, we calculated that diarrhea was associated with a shift in length distributions that resulted in a 13% increase in the prevalence of stunting (from 31% to 35%).

DISCUSSION

Using this large, multisite data set, we comprehensively evaluated the longitudinal association between diarrhea and linear and ponderal growth. By utilizing detailed diarrhea histories for each anthropometric measurement, we were able to calculate the short- and long-term relationships between diarrhea in early childhood and growth. Diarrhea has a short-term negative association with weight, as confirmed by the...
velocity model and by the lagged model that showed a negative relationship between diarrhea and weight only when the diarrhea was experienced in the past 30 days. The association between diarrhea and length, however, is more complex. When we used LAZ at a single point in time as the outcome variable as a function of diarrhea burden, 4 of the 7 studies had confidence intervals that overlapped zero, indicating a potentially weak overall relationship between diarrhea and growth. Length velocity over a 4-month period was similarly inconclusive. Days with diarrhea during individual months had little apparent relationship with linear growth. When cumulative diarrhea effects were calculated using the lagged model, however, we demonstrated a small but measurable association between diarrhea burden and linear growth. Therefore, we conclude that any single episode of diarrhea during childhood has a small relationship with linear growth that can be recovered through catch-up growth, given adequate illness-free time; however, when accumulated throughout the first 24 months of life, diarrhea has the potential to be associated with a loss in height potential.

We expected to observe a short-term (1-month) association between diarrhea and ponderal growth, and this was observed at most ages in the lagged diarrhea model. Weight at the youngest months of age appeared to be less affected by diarrhea, perhaps because breastfeeding provides some protection from weight faltering. It has been demonstrated that intake of breast milk during diarrhea episodes continues at the same pace, while intake of other foods decreases (41, 42); therefore, diarrhea may have more of an impact in children who are partially or completely weaned. Diarrhea appears to have little, if any, long-term association with weight.

When considered as part of a larger model examining the relationship between any diarrhea during specific lagged months and length from 1 to 24 months of age, there appeared to be little indication of a lagged association between diarrhea and length. When a child experiences weight faltering, it is thought that the child regains weight at the expense of length acquisition (43). Once a child recovers weight, catch-up growth in length is expected if there are no further nutritional insults. The results of this analysis indicate that diarrhea in a single month does not have a large measurable relationship with length 1, 2, or 3 months later; however, it is likely that the cumulative burden of diarrhea in conjunction with other factors is associated with linear growth faltering. When we considered the cumulative relationship between different levels of diarrhea and linear growth, the relationship became more evident. Although the absolute differences in length appear small, these associations, in conjunction with poor food quality and/or quantity and inadequate access to health care, are all likely to contribute to the high levels of stunting observed in some developing countries.

Although we attempted to adjust for differences among study sites and individuals within those study sites by using random-effects methods, there are many factors that may have influenced our findings, including differences in data collection methods, measurement accuracy, and supervision and training of the field staff. SES is a major potential confounder in the relationship between diarrhea and growth, since children from families with lower SES may have lower LAZ and higher diarrhea burdens than families with higher SES. Although we did not have comparable indicators of SES across the different studies, all of the studies were performed in low-SES areas, and we included baseline LAZ in our models to control for this potentially confounding relationship. In addition, there are a number of different factors that may modify these relationships, including dietary intake (including breastfeeding), access to health care, other infectious diseases, season, and the diarrhea etiologies specific to the study sites. However, it is the strength of the numbers that allows us to discern the small yet measurable long-term association between early diarrhea and linear growth. Future large multisite studies with harmonized protocols will allow for further investigation of these important relationships, including quantification of the attributable effects of diarrhea along with other infectious diseases, diet, and breastfeeding. Given the subtle relationship between diarrhea and linear growth observed in this study, it is not surprising that the literature on this topic is so varied. The association between diarrhea and linear growth may be reduced due to catch-up growth; therefore, a better understanding of the process of catch-up growth would be a worthwhile contribution to the literature. Programs to improve dietary intake or provide nutritional supplementation have been shown.
to offset the detrimental association between diarrhea and length (20, 21, 44). Diarrhea is one of the main causes of preventable early childhood death (45); therefore, diarrhea prevention in developing countries should be a public health priority.

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REFERENCES


