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Frequency of diarrhoea as a predictor of elevated blood pressure in children

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Abstract

Background—Diarrhoeal illness is a major public health problem for children worldwide, particularly among developing countries, and is a proxy condition for severe dehydration. It has been hypothesized that severe dehydration in the first 6 months of life could be associated with increased blood pressure later in life. This study aimed to explore whether frequency of diarrhoea is associated with elevated blood pressure in children in a setting with a high incidence of diarrhoeal disease.

Methods—The present study is a cross-sectional study of blood pressure among children from a longitudinal child diarrhoeal disease cohort in Lima, Peru. From 2001 to 2006, daily diarrhoeal

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J.J.M., G.D.S., L.S., R.H.G. and H.H.G. conceived the idea and were part of study design. L.C., Y.R.O., V.A.C., H.H.G. and R.H.G. conducted the diarrhoeal cohort study and J.J.M. was responsible for the blood pressure study. A.R.D., J.J.M. and V.A.C. took part in data analysis. J.J.M. and A.R.D. wrote the first draft of the article. All authors contributed to data interpretation and writing-up of subsequent versions of the article.

We declare that we have no conflicts of interest. The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the CDC.

surveillance was made. Children were revisited in 2006 and blood pressure was measured. Diarrhoeal exposures were evaluated in terms of total number of diarrhoea days, number of episodes of diarrhoea, persistent diarrhoeal episodes and by the quartiles of daily incidence and episode incidence of diarrhoea.

Results—The overall incidence of diarrhoeal episodes at age under 1 year was 4.35 (95% confidence interval: 3.79-4.98) and under 5 years was 2.80 (95% confidence interval: 2.69-2.92). No association was observed between the total number of diarrhoeal days, diarrhoeal episodes or diarrhoeal incidence rates with childhood blood pressure. There was weak evidence that hospital admission due to severe dehydration in the first year of life showed a gradient towards an increase in both, systolic and diastolic blood pressure.

Conclusion—In the first study to date to examine the association in a setting with a high incidence of diarrhoeal disease, diarrhoeal frequency did not show an association with increased blood pressure. Our observations of elevated levels of blood pressure among those admitted into hospitals in the first year of life are in line with the original hypothesis of dehydration in early infancy and high blood pressure. However, the effect of episodes of severe dehydration on later blood pressure remains uncertain.

Keywords

blood pressure; child; cohort studies; dehydration; developing countries; hypertension; infantile diarrhoea; Peru

Background

Globally, hypertension represents a major preventable risk factor in terms of cardiovascular health [1]. Latin America and the Caribbean regions present a high prevalence of hypertension, particularly in the male population [2]. Hypertension in adulthood can be traced back to childhood and early life factors [3,4], and there is good evidence that elevated blood pressure (BP) in children is a strong predictor of high BP levels in adulthood [5,6]. In adults, the disease condition most strongly associated with high BP is haemorrhagic stroke and this disease also shows a relationship with adversity in early life [7]. Evaluating conditions associated with elevated BP in childhood could provide insights into the understanding of adult hypertension and its complications and contribute towards the advancement of new tools to address hypertension at the population level, particularly in developing countries.

Recently, it has been hypothesized that severe dehydration in the first 6 months of life could be associated with increased BP later in life [8,9]. This observation has been interpreted as resulting from developmental plasticity; in this case, the physiology of infants reacting to an episode of dehydration by moving towards a salt-retention state, which would reduce the consequences of further severe dehydration episodes and thus have a survival advantage [10,11].

Diarrhoeal illness, a major public health problem for children worldwide [12,13], is a proxy condition for severe dehydration. Taking advantage of established cohorts in developed countries, recent reports have explored the association between diarrhoea in childhood and BP later in life [14,15], as well as its association with coronary heart disease mortality [16]. Building upon previous field experience on diarrhoeal research in Peru [17-21], this study aims to explore whether or not frequency of diarrhoea is associated with elevated BP in children.

Methods

Study design and setting

The present study is a cross-sectional study of BP among children from a longitudinal child diarrhoeal disease cohort. The population studied was drawn from a prospective cohort study conducted from 2001 to 2006, which aimed to ascertain cases of infections with enteric pathogens in children living in the community Pampas de San Juan de Miraflores, in Lima, Peru. Following a baseline census, one index-case child per household, aged under 10 years was enrolled in the cohort. The main exclusion criterion was the diagnosis of severe acute malnutrition. This was identified by anthropometric measurements as having weight-for-height indicator with Z -scores below -2 , according to the 2000 Centers for Disease Control and Prevention (CDC) Growth Charts [22]. Gastrointestinal manifestations, including frequency and consistency of stools per day, were collected on a daily basis. Stool samples, to evaluate the presence of specific enteric pathogens, were collected on a weekly basis and whenever the study participant reported a diarrhoeal episode. Anthropometric measurements (weight and height) were collected at 1-month intervals on the day of their birth dates. Data on socioeconomic status were collected in structured questionnaires at time of enrolment.

For epidemiological accuracy, we analysed all data only from participants who had at least 6 months of participation in the study and at least 80% compliance with the study procedures. Four hundred and ninety-three participants met this definition and all their data were included in statistical analyses for this study. BP follow-up study was conducted from September to December 2006 among these 493 children.

Measurements

Birth weight, birth length, socioeconomic information expressed as household bedroom ratio (ratio of the number of household residents per bedroom) and maternal education were obtained from the baseline datasets. Data on the number of stools per day, stool consistency and whether the child had received oral rehydration therapy (ORT) were obtained from the daily diarrhoeal surveillance dataset.

BP and skin-fold (triceps, biceps, subscapular and suprailiac) measurements were recorded in triplicate. Single measures of leg length, height and weight were recorded in all those who agreed to participate in the follow-up study. Parents were asked to recall whether the child had been admitted into hospital for dehydration either during the first year of life or ever, and the number of occasions admitted in those periods. Sex, date of birth and date of evaluation were also recorded.

Skin-fold thickness was calculated as the sum of the mean values of all four individual skin-fold measurements. If one of the four values was missing, then the skin-fold value was treated as missing. BMI was calculated as $\text{weight}/\text{height}^2$. Height-for-age Z -scores were calculated on the basis of CDC 2000 growth standards references [22].

Height and weight were measured using standardized methods. Measurements were taken with the participants clothed and without shoes. Standing height was determined, without shoes, using a stadiometer, accurate to the nearest 0.1 cm. Weight was measured using an electronic scale and recorded to the nearest 0.1 kg. Leg length was measured in standing position without shoes, from the floor to greater trochanter and recorded to the nearest 0.1 cm.

BP was taken with a mercury sphygmomanometer (Nova Presameter, Riester, Germany), recognized to be the gold standard instrument for paediatric measurements [23]. Systolic and

diastolic BPs (SBP and DBP) were based on the first and fifth Korotkoff phases, respectively. For each child, three BP measurements were recorded and these were taken at least 5 min apart. The study investigators ensured that children had not exercised before the test and were resting when measurements were made. All BP measurements were taken in the sitting position with the right arm supported at chest level. Cuff sizes of 23×7.2 and 33.5×10 cm were used and the appropriate cuff size was selected with a bladder width that was approximately 40% of the arm circumference, mid-way between the olecranon and the acromion. The cuff covered 80-100% of the arm circumference [23]. The mean of the last two BP measurements was used to estimate mean SBP and mean DBP in each child.

Diarrhoeal exposure

A day with diarrhoea was defined as any day in which a participant had three or more liquid or semiliquid stools. An episode of diarrhoea started on a day when a child had diarrhoea and ended on the last day with diarrhoea, which was followed by 3 or more days without diarrhoea [24,25]. The length of a diarrhoeal episode was considered as a marker of severe diarrhoeal cases because of the impact of longer diarrhoeal episodes on child mortality and malnutrition [26,27]. The rate of persistent diarrhoea was defined as the number of episodes of 14 days or more per child-years of follow-up [28]. The presence of blood in stool was reported in 1.7% of days with diarrhoea. Exploratory analyses indicated these days were sporadic and not indicative of an established diarrhoeal episode due to infection. Therefore, no distinction between diarrhoea and diarrhoea in the presence of blood was made in the final analyses.

Diarrhoeal exposure was evaluated in two ways: diarrhoea based on daily surveillance of gastrointestinal symptoms and hospital admission based on parent's information of hospitalizations due to diarrhoea. Diarrhoeal exposure was analysed at two life periods: during the first year of life and within the first 5 years of life. Diarrhoeal exposures were evaluated in terms of total number of diarrhoea days, number of episodes of diarrhoea, persistent diarrhoeal episodes and by the quartiles of daily incidence and episode incidence of diarrhoea.

Statistical analyses

Individual child-years of follow-up were used to calculate incidence rates. The observation period was from date of entry into the cohort study to date of the last diarrhoeal surveillance. If the child had diarrhoea on the date of entry, the observation start date was set to the entry date minus 0.5 day. The longitudinal daily incidence of diarrhoea was calculated as the number of days with diarrhoea per child-years of follow-up. The episode incidence was calculated as the number of episodes of diarrhoea per child-years of follow-up [29]. For all rates, 95% confidence intervals (CIs) were provided.

A regression model was used to investigate the association between exposure, as defined above, and SBP and DBP. Each potential explanatory variable (age, sex, weight and length at birth, height-for-age Z-score, BMI, skinfold, leg length, household bedroom ratio quartile and maternal education) was first analysed in univariate regression models and the regression coefficients (95% CI) determined. To adjust for the effects of potential confounders, each variable observed to be associated with BP in the univariate analysis was added to the multivariate regression model and the effect was evaluated with a likelihood-ratio test. Regression coefficients and the 95% CI were reported. Statistical analyses were performed using Stata software version 9 (Stata Corporation, College Station, Texas, USA).

Ethical considerations

Both, children and a parent gave consent prior to the taking of any measurement. Ethical approval for the BP assessment was obtained from Universidad Peruana Cayetano Heredia's ethics committee. The diarrhoeal surveillance project received ethical approval from Universidad Peruana Cayetano Heredia and Asociación Benéfica PRISMA in Peru, and by Johns Hopkins Bloomberg School of Public Health, University of Georgia and CDC in the USA.

Role of the funding source

The funding institutions did not have a role in study design, data collection, analysis and interpretation of the data, nor in the decision to submit this article for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 493 children with diarrhoeal surveillance, in 422 (85.6%) consent was obtained from their parents and, in some cases, the children themselves (if 5-year-old or older) also assented to participate in the follow-up study on BP (Fig. 1). There was no sex (χ^2 $P=0.712$) or age (χ^2 $P=0.134$) difference between participants and non-participants.

Diarrhoea

The 422 children (48.3% male children) contributed a total of 1222.3 child-years of follow-up (mean 2.9, range 0.5–4.5 child-years); 92.9% of the children had one or more days with diarrhoea during the observational period. A total of 5212 diarrhoea days equating to 2624 diarrhoeal episodes were recorded (Fig. 1).

Daily incidence was 4.26 days per child-years (95% CI 4.15–4.38) and episode incidence was 2.15 (95% CI 2.07–2.23) episodes per child-years. Daily and episode incidence rates were highest at age less than 1 year and decreased with increasing age (Table 1). Fifty-five percent of episodes recorded lasted 1 day, 30.3% for 2–3 days, 11.6% for 4–6 days, 3.2% for 7–13 days and 0.3% for 14 days or more. The mean episode duration was longest at age less than 1 year [2.4 days (95% CI 2.1–2.7)] and episode duration decreased with increasing age. Overall, the mean episode duration was 2.1 days (95% CI 2.1–2.2). One child had an episode of persistent diarrhoea during his/her first year of life (rate within first year of life: 0.02 episodes (95% CI 0.003–0.15 per child-years) and a total of eight children had persistent diarrhoea during their first 5 years of life [rate within first 5 years of life: 0.01 episodes (95% CI 0.01–0.02)].

Blood pressure

The mean age of the 422 children at the BP measurement was 5.6 years (SD 2.4 years) and ranged from 1 to 13 years. The mean SBP and DBP were 99.1 (95% CI 98.1–100.1) and 62.7 mmHg (95% CI 61.8–63.6), respectively. There was no evidence of a sex difference in SBP ($P=0.152$) or DBP ($P=0.535$). In the univariate analysis, there was evidence of a strong positive correlation between BP and increasing age, with a single year increase in age equating to 1.83 mmHg (95% CI 1.46–2.19, $P<0.001$) increase in SBP and 1.02 mmHg (95% CI 0.68–1.36, $P<0.001$) increase in DBP. Of the variables recorded at the time of the BP measurement, univariate analysis indicated evidence of a positive correlation between height-for-age Z-scores, leg length, BMI and skin-fold thickness with BP. There was no evidence of a correlation between household bedroom ratio or maternal education and BP. There was no evidence of a correlation between variables recorded at birth (birth weight and

length) and BP, but this could be due to the high proportion (>70%) of missing values for information at birth.

Seventeen of the 422 children were ever hospitalized for dehydration, nine of whom were hospitalized in their first year of life. Univariate regression analysis provided weak evidence of 1.4 mmHg higher DBP (95% CI -4.5-7.4) and 5.5 mmHg higher SBP (95% CI -1.4-12.3) among those who were hospitalized for dehydration in the first year of life. After adjusting for possible confounders, these effects were attenuated (Table 2). Nine children received ORT during their first year of life. There was no evidence of a correlation between ORT and BP (Table 2). In univariate and multivariate analysis, there was no evidence of a difference in SBP or DBP with hospitalization for dehydration or receiving ORT ever during follow-up (results not shown). In addition, there was no evidence in a univariate and multivariate analyses to suggest that an episode of persistent diarrhoea during the first 5 years of life was associated with BP.

A total of 104 children contributed to the diarrhoeal surveillance data during their first year of life. Differences in SBP and DBP by exposure defined as diarrhoeal incidence in the first year of life are shown in Table 3. There was no evidence in crude or adjusted regression analysis to suggest a linear relationship between the number of diarrhoea days or number of diarrhoeal episodes in the first year of life and DBP or SBP. Nor was there evidence to suggest that increases in the incidence of diarrhoea in the first year of life were associated with DBP or SBP.

A total of 376 children contributed to the diarrhoeal surveillance data up to the age of 5 years. After adjusting for confounding factors, there was no evidence of an association of the number of days, episodes or increases in the incidence of diarrhoea in the first 5 years of life with DBP or SBP (Table 3).

Discussion

The cohort studied showed a high endemicity of diarrhoea among children with high incidence of diarrhoeal episodes in children less than 2 years. In the first year of life, the incidence of diarrhoeal episodes was 4.4 per child-years, which is above the median of 3.9 episodes per child-year described internationally among this age group [12] and similar to other settings like neighbouring Brazil [29]. Among all children, the rate of persistent diarrhoea was 0.01 episodes per child-year, similar to that found by previous reports from Peru [30].

Currently, diarrhoea is a condition of particular relevance for public health in developing countries due to its impact on child morbidity and mortality [13]. Diarrhoea is also of utmost importance to Peru, a country that reported the initial cases of a cholera epidemic that affected Latin America in the early 1990s [31]. In terms of mortality, diarrhoeal illnesses and pneumonia account for 30% of all mortality in under 5-year-old population in Peru [32]. The possibilities of exploring linkages between diarrhoeal diseases in children and other conditions that are expressed later in life could be beneficial for two reasons: first, it reassures the contributing role of diarrhoea to morbidity throughout the life period and not only during childhood; and, second, it could contribute to the understanding of other conditions more common in adulthood such as high BP and stroke mortality that nowadays are strongly affecting low-income and middle-income countries [33].

It could be argued that current mortality patterns observed in some developing countries resemble those of industrialized countries several decades ago, with high levels of infant mortality and poor hygiene conditions. An ecological analysis has shown that infant mortality 70 years ago in industrialized countries has a strong correlation with current stroke

mortality [34]. A common early life exposure in these settings is infant diarrhoea, a cause and a marker of infant dehydration. A recent study by Davey Smith *et al.* [8] and Lawlor *et al.* [9] hypothesized that severe dehydration in the first 6 months of life could be associated with increased BP later in life. This observation was interpreted as resulting from developmental plasticity; in this case, the physiology of infants reacting to an episode of dehydration by moving towards a salt-retention state, which would reduce the consequences of further severe dehydration episodes and thus have a survival advantage [10,11]. Going a step further, a randomized controlled trial has shown that salt restriction, an accepted and indicated step in the management of adult hypertension [35], administered in childhood during the first 6 months of life was related to lower BP at age 15 [36]. Mean SBP and DBP were markedly lower among the group originally randomized to the low-salt group compared with the high-salt group: mean difference in SBP was 3.6 mmHg and in DBP was 2.2 mmHg [36].

Dehydration could lead, through different mechanisms, to elevated BP in childhood, which could be sustained into adulthood. Elevated BP in adulthood is strongly linked to stroke, particularly haemorrhagic stroke. And, stroke patterns of today's industrialized countries correlate strongly with infant mortality decades ago, when diarrhoeal illnesses were an important mortality contributor. Therefore, it is plausible to propose and to explore whether children exposed to high levels of diarrhoea frequency in a developing country setting experience elevated BP.

Our frequency of diarrhoea data, using different exposure approaches -including number of days of diarrhoea, number of episodes and diarrhoeal incidence - did not show a consistent pattern of association with childhood BP. In the unadjusted and adjusted analyses, there was a lack of association between the different parameters of diarrhoea used and BP for both 1-year and 5-year-old groups.

Similar observations, a lack of association between diarrhoeal episodes and BP or mortality later in life, have recently been reported by Batty *et al.* [14,16] and Pearce *et al.* [15] in larger cohorts. These studies from the United Kingdom provide an advantage of a long-term follow-up to explore the association of interest with an outcome later in life in adulthood. However, these reports focused on a dichotomization (yes/no) of childhood diarrhoeal episodes. Our study goes further in reporting diarrhoeal exposure as number of diarrhoea days, number of episodes of diarrhoea and by exploring the quartiles of daily incidence and episode incidence of diarrhoea. Nonetheless, participants were quite young when studied. It is possible that it might take longer and later in life to observe an increase in BP. It might be only at an older age, when other adding causes of hypertension are present as well (cumulative risk) that early episodes of diarrhoea and dehydration play a role.

However, although a small number of cases, there was weak evidence that hospital admission due to dehydration in the first year of life shows a gradient towards an increase in both, SBP and DBP. These observations are in line with the original hypothesis of dehydration in early infancy and high BP [8]. Davey Smith *et al.* [8] showed, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study of children aged 7 years old in the United Kingdom, that mean BP values were higher among children admitted to hospital due to dehydration. Nonetheless, the ALSPAC cohort data showed that this association was more robust for DBP. This result was not replicated in our study, which showed weak evidence of association for both, SBP and DBP, but differences were greater in SBP. Higher differences in SBP have also been shown by Lawlor *et al.* [9] using climate data during the first year of life as a surrogate marker of environmental conditions associated with diarrhoea and dehydration. Based on the small numbers observed

in our study, it would be inappropriate to elaborate on the strengths or weaknesses of these associations, and more robust evidence is required to corroborate or refute these findings.

Despite the major strength of this study in terms of detailed assessment of diarrhoeal frequency and patterns, some limitations have to be considered. Information about hospital admission due to diarrhoeal dehydration was evaluated through a questionnaire. Hospital records were not available to assess the severity of such episodes and the treatment provided. However, hospital admission of an infant is a traumatic event for the child's family and may not suffer from serious recall bias due to under or over ascertainment of cases. ORT could also signal us towards the severity of a particular diarrhoeal episode. This information, together with other medication received, was gathered during the daily diarrhoeal surveillance of the cohort. However, due to the strong impact of the cholera epidemic in Peru and years of work in rehydration therapy in the country, ORT has become a common therapeutic tool widely used at the community level [37], thus limiting its interpretation as a marker of a severe diarrhoeal episode.

Among a population of children with high levels of diarrhoea, we found no evidence to support the hypothesis that diarrhoeal disease without severe dehydration is subsequently associated with elevated BP. However, the effect of episodes of severe dehydration on later BP remains uncertain.

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Abbreviations

BMI	body mass index
BP	blood pressure
CDC	Center for Disease Control and Prevention
CI	confidence intervals
DBP	diastolic blood pressure
ORT	oral rehydration therapy
SBP	systolic blood pressure

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Fig. 1.
Summary of the baseline population and the number of diarrhoea days and episodes.

Table 1
Number of days with diarrhoea, number of diarrhoeal episodes, incidence and prevalence of diarrhoea per child-years, by age at diarrhoea onset

Age (years)	Follow-up time (child-years)	Number of patients ^a	No. of days with diarrhoea	Prevalence per child-years (95% CI)	No. of diarrhoeal episodes	Incidence per child-years (95% CI)
<1	47.41	104	444	9.37 (8.53-10.28)	206	4.35 (3.79-4.98)
1	155.65	218	1514	9.73 (9.25-10.23)	709	4.56 (4.23-4.90)
2	216.51	274	1397	6.45 (6.12-6.80)	682	3.15 (2.92-3.40)
3	207.08	281	808	3.90 (3.64-4.18)	405	1.96 (1.77-2.16)
4	173.22	220	414	2.39 (2.17-2.63)	238	1.37 (1.21-1.56)
5+	422.45	203	635	1.50 (1.39-1.62)	384	0.91 (0.82-1.00)
<5	799.87	376	4577	5.72 (5.56-5.89)	2240	2.80 (2.69-2.92)
All ages	1222.32	422	5212	4.26 (4.15-4.38)	2624	2.15 (2.07-2.23)

95% confidence intervals (CI) provided.

^aTotal not equal to 422 as children move through the age groups.

Table 2
Univariate and adjusted linear regression analysis presenting mean systolic and diastolic blood pressure according to hospitalization for dehydration or oral rehydration therapy in the first year of life and the regression coefficients

		Diastolic blood pressure			Systolic blood pressure		
		Univariate		Adjusted ^a	Univariate		Adjusted ^a
N		Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Hospitalized for dehydration in first year of life							
No	413	61.2 mmHg		55.0 mmHg		93.5 mmHg	
Yes	9	1.4 (-4.5-7.4)	0.633	0.3 (-6.2-6.7)	0.932	5.5 (-1.4-12.3)	0.116
Number of times hospitalized in first year of life							
0	413	62.7 mmHg		55.3 mmHg		98.9 mmHg	
1	8	0.0 (-6.3-6.3)	0.990	-0.9 (-7.8-6.1)	0.800	4.1 (-3.2-11.3)	0.273
2	1	13.3 (-4.3-31.0)	0.139	7.5 (-9.5-24.5)	0.385	17.1 (-3.3-99.9)	0.100
Received ORT in first year of life							
No	413	62.8 mmHg		55.8 mmHg		99.1 mmHg	
Yes	9	-3.7 (-9.6-2.3)	0.227	-3.2 (-9.4-3.0)	0.315	-1.3 (-8.2-5.6)	0.707
Hospitalized or ORT							
No	406	62.7 mmHg		55.3 mmHg		99.0 mmHg	
Yes	16	-1.0 (-5.5-3.5)	0.669	-1.5 (-6.1-3.2)	0.541	2.7 (-2.5-7.9)	0.303
						76.4 mmHg	0.285

P values from regression analyses provided. CI, confidence interval; ORT, oral rehydration therapy.

^a Adjusted for sex, age at blood pressure measurement, height-for-age Z-score, BMI, skin fold and leg length.

Table 3
Univariate and adjusted linear regression analysis investigating the relationship between diarrhoeal exposure at different ages and diastolic and systolic blood pressure at follow-up

	Diastolic blood pressure				Systolic blood pressure			
	Univariate		Adjusted ^a		Univariate		Adjusted ^a	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Diarrhoeal exposure up to age 1 year (<i>n</i> =104)								
No. of diarrhoea days								
0-30 ^b	0.1 (-0.1-0.4)	0.354	0.1 (-0.2-0.4)	0.452	-0.2 (-0.4-0.1)	0.172	-0.2 (-0.5-0.1)	0.173
Daily incidence								
Quartiles ^c	0.1 (-1.2-1.4)	0.862	-0.1 (-1.6-1.4)	0.884	-0.4 (-1.5-0.8)	0.518	-0.6 (-1.9-0.7)	0.346
No. of diarrhoeal episodes								
0-13 ^b	0.2 (-0.5-0.9)	0.543	0.1 (-0.7-1.0)	0.743	-0.4 (-1.0-0.2)	0.232	-0.4 (-1.1-0.3)	0.215
Episode incidence								
Quartiles ^c	0.2 (-0.8-1.8)	0.467	0.3 (-1.2-1.8)	0.708	-0.0 (-1.2-1.1)	0.946	-0.4 (-1.7-0.9)	0.566
Diarrhoeal exposure up to age 5 years (<i>n</i> =376)								
No. of diarrhoea days								
0-111 ^b	-0.1 (-0.1-0.0)	0.004	0.0 (-0.1-0.0)	0.221	-0.1 (-0.1-0.0)	0.013	0.0 (-0.1-0.0)	0.272
Daily incidence								
Quartiles ^c	-1.4 (-2.2--0.6)	0.001	-0.7 (-1.6-0.1)	0.086	-0.9 (-1.8--0.1)	0.027	-0.2 (-1.0-0.7)	0.696
No. of diarrhoeal episodes								
0-33 ^b	-0.2 (-0.4--0.1)	0.010	-0.1 (-0.3-0.1)	0.285	-0.2 (-0.3-0.0)	0.033	0.0 (-0.2-0.1)	0.603
Episode incidence								
Quartiles ^c	-0.9 (-1.7--0.2)	0.017	0.0 (-0.3-0.4)	0.813	-0.9 (-1.7-0.0)	0.040	-0.1 (-0.5-0.3)	0.692
Episode of persistent diarrhoea ^d	-3.6 (-9.7-2.5)	0.245	-1.4 (-7.9-5.0)	0.664	-4.3 (-10.7-2.1)	0.185	-3.5 (-9.9-2.9)	0.279

Regression coefficients, 95% confidence intervals (CI) and *P* values provided.

^a Adjusted for sex, age at blood pressure measurement, height-for-age Z-score, BMI, skinfold and leg length.

^b For each single unit increase.

^c For each increase in quartile.

^d Compared to not having an episode of persistent diarrhoea.

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