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Malnutrition-related early childhood exposures and enamel defects in the permanent dentition: A longitudinal study from the Bolivian Amazon

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Abstract

Objectives—We investigated the relationship between early childhood malnutrition-related measures and subsequent enamel defects in the permanent dentition.

Materials and Methods—This cohort study included 349 Amerindian adolescents (10–17 years, 52% male) from the Bolivian Amazon. Exposures included: stunted growth (height-for-age z-scores), underweight (weight-for-age z-scores), anemia (hemoglobin), acute inflammation (C-reactive protein) and parasitic infection (hookworm). We measured the occurrence (no/yes) and extent (<1/3, 1/3–2/3, >2/3) of enamel defects. We estimated associations between childhood exposures and enamel defect measures using log-binomial and multinomial logistic regression.

Results—The prevalence of an enamel defect characterized by a cobblestone-like depressed surface of deficient enamel thickness on the labial surface of the central maxillary incisors was 92.3%. During childhood (1–4 years), participants had a high prevalence of stunted growth (75.2%), anemia (56.9%), acute inflammation (39.1%), and hookworm infection (49.6%). We observed associations between childhood height-for-age (OR=0.65; p=0.028 for >2/3 extent vs. no EH) and gastrointestinal hookworm infection (OR=3.43; p=0.035 >2/3 extent vs. no defects or <1/3 extent) with enamel defects.

Discussion—The study describes a possibly novel form of enamel hypoplasia and provides evidence for associations of malnutrition-related measures in early childhood, including stunted growth and parasitic helminth infection, with the observed enamel defects.

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Contributions of authors

Masterson conceived of and designed the present study, collected and analyzed the data, interpreted findings, and drafted the present manuscript. Fitzpatrick, Enquobahrie, Manc and Hujoel contributed to the conception and design of the study, interpretation of the findings and drafting the present manuscript. Conde led the intensive data collection required for this study. All authors have critically revised and given their final approval of the submitted manuscript.

Keywords

Stunted Growth; Parasitic Worms; Infectious Diseases; Dental Enamel Defects

The dental enamel in the permanent dentition starts to mineralize shortly after birth (Massler et al. 1941; Sarnat and Schour 1941). Developmental defects in the permanent dental enamel result from local, systemic and genetic factors that disrupt the enamel formation process prior to eruption. These developmental defects may lead to post-eruptive enamel defects, including erosion, and dental caries in the permanent dentition (Psoter et al. 2005; Taji and Seow 2010; Caufield et al. 2012). The mineralization process to form enamel is highly-sensitive to environmental and physiological stressors and resulting defects are not repaired during the life course (Sarnat and Schour 1941; Pindborg 1982; Goodman and Rose 1990). In this way, teeth may serve as permanent records of early life events or exposures. Enamel hypoplasia (EH), one particular type of developmental defect, is caused by disruption to the early, secretory phase of enamel formation when layers of the enamel matrix are being formed, which permanently results in deficient enamel thickness (Sarnat and Schour 1941; Pindborg 1982; Laskaris 2003). EH is sub-classified based on its appearance, commonly horizontal grooves, pits or missing enamel in the tooth surface (Clarkson and O'Mullane 1989; Health 1992; Hillson 2014).

The prevalence of developmental enamel defects in the permanent dentition varies greatly across and within populations. A disproportionate burden of defects is shouldered by marginalized, low-income populations (Psoter et al. 2005; Golkari et al. 2016). There is evidence that systemic factors associated with developmental enamel defects include disease, macronutrient and micronutrient deficiencies, chronic conditions, excessive fluoride exposure, and/or prolonged use of certain medications. Developmental enamel defects may also be caused by genetic and local intra-alveolar factors, such as primary tooth infection and trauma/injury to the primary dentition (Mellanby 1927; Sarnat and Schour 1941; Pindborg 1982; Goodman and Rose 1990; Seow 1991; Laskaris 2003; Golkari 2009; Skinner et al. 2014). Developmental defects in the permanent dentition are thus generally interpreted as a non-specific indicator of metabolic disruption and physiological stress during early childhood (Rose et al. 1978; White 1978; Goodman and Rose 1991; Floyd 2007).

Few human studies have the follow-up time required to prospectively study factors related to relate early post-natal stressful exposures and their impact on the occurring enamel formation in the *permanent* dentition, which can only be observed *in vivo* when the teeth start erupting at the age of 6 years (ADA 2006). Studies that have assessed growth stunting and absence of nutritional supplementation have concluded that children who are short for their age and who are undernourished are significantly more likely to have defects in their permanent dentition (Goodman et al. 1991; Rugg-Gunn et al. 1997; Zhou and Corruccini 1998; Santos and Coimbra 1999). The current study applied prospectively-collected, longitudinal data that span 13 years to investigate associations of specific post-natal stressors with subsequent enamel defects in the permanent dentition.

MATERIALS AND METHODS

Study design and sample

This current study was based on a prospective cohort study that began in 2002, the 9-year Tsimane' Amazonian Panel Study (TAPS) (Leonard et al. 2015). In 2015, researchers followed up a sample of adolescents, aged 10–17 years, who were enrolled as young children (between 1 and 5 years) in TAPS and added measures of enamel defects in the permanent dentition. Criteria for inclusion in the follow-up study include being 10–17 years of age at the time of data collection (so that the central maxillary incisors will have fully erupted), enrollment in TAPS for at least one year when aged 5 years or less, and residence in one of 15 communities visited by the data collection team during the 2015 follow-up study.

The study sample was derived from the Tsimane' population, an Amerindian group of approximately 17,000 people who live across more than 100 small, remote communities, accessible by dirt roads and/or canoe and river in Bolivia's Amazonian Basin (NIE 2012). Although they are increasingly integrated into mainstream Bolivian society and exposed to the market economy and a Western diet, the Tsimane' maintain, in part, a traditional hunter-horticultural lifestyle and primarily speak their native language in their communities. The original TAPS study included 1,453 participants, 655 of whom were eligible for the 2015 follow-up study. 349 participants were enrolled in the 2015 follow-up study. The sample was further reduced to 337 due to 12 participants with missing or severely decayed central maxillary incisor (which makes enamel defect measurement impossible). Of these participants, 327 participants had at least one year of childhood anthropometric (height and weight) data that correlated with the etiologically-relevant exposure period for the study outcome (ages 1 through 4 years).

Approval for all data collection and use was obtained from the local tribal government, the *Gran Consejo Tsimane'* (GCT, Tsimane' Grand Council) and the University of Washington (UW) Human Subjects Division (HSD). Informed consent was obtained from participants who were 16–17 years of age and married, whereas for those not married and/or those less than 16y, assent and parental permission were obtained according to the approved UW HSD protocol.

Exposures

The primary exposures of interest for the present analysis were collected during early childhood and include: stunted growth (an indicator of chronic malnutrition), underweight (an indicator of acute malnutrition), anemia, acute inflammation, and parasitic gastrointestinal infection (indicators of general health and infection). Based on histological evidence (Reid and Dean 2006), enamel on the permanent central maxillary incisors is formed when the child is 1 through 4 years old. When the child is 1 year old, the enamel is being formed at the incisal edge of the central incisor. When the child is 4 years old, the enamel in the cervical part (the part close to the gingiva) is being formed. Since the permanent central maxillary incisors were the teeth of focus in this analysis, childhood exposure measures were restricted to 1 through 4 years of age. Childhood data were

collected annually by the TAPS study team between 2002 and 2010 (Leonard et al. 2015). Growth stunting was measured on a continuous scale using mean height-for-age z-scores (HAZ) from 1 through 4 years of age. Similarly, underweight was measured on a continuous scale using mean weight-for-age z-scores (WAZ) from 1 through 4 years of age. Both HAZ and WAZ were age- and sex- standardized according to National Center for Health Statistics (NCHS) growth charts, the international reference reported by other TAPS publications. A threshold of <-2.0 z-score was used to dichotomize stunted vs. normal average height, and, underweight vs. normal average weight during early childhood. Anemia was measured on a continuous scale by measuring hemoglobin (Hb; in g/dL) using dried blood spots (in 2002 and 2003) for a sub-sample of 79 participants (McDade et al. 2005). Immune activation was measured on a continuous scale by measuring C-reactive protein (CRP; in mg/L) using dried blood spots for a sub-sample of 72 study participants (in 2002–2003). Standard age- and sex-based reference values for clinical practice were used to determine thresholds for anemia and elevated CRP (acute inflammation) classification (Mayo Clinic 2015). Finally, parasitic infection was determined based on assessment of fecal samples from a sub-sample of 115 study participants (in 2003 and 2007) (Tanner et al. 2009; Tanner et al. 2013). Children were classified as infected vs. not by presence or absence of any hookworm in fecal samples.

Outcome

The outcome of interest in these analyses was enamel defects in the permanent central maxillary incisors. These defects were captured through digital intraoral photographs with a macro lens and ring flash, detected using Photoshop software, and quantified according to the internationally-accepted DDE Index/Modified DDE Index (Clarkson and O'Mullane 1989; FDI 1992). Enamel defects were measured in the two central maxillary incisors because defects were measured most reliably in photographs. The results of this analysis focused on the most prevalent defect pattern observed on the labial surface of the maxillary incisors in this study sample. We classified the teeth of interest according to the Modified DDE Index, by occurrence (any, none) and extent of tooth surface (less than 1/3, 1/3 to 2/3, or more than 2/3) affected by enamel defects. These measures were recorded based on findings of assessment of the left central maxillary incisor or – if the left was missing or severely decayed– of the right central maxillary incisor. There was 93.4% concordance of EH occurrence between the two central maxillary incisors.

Covariates

Covariate measures from the TAPS 2002–2010 dataset, including sex (male/female), age (measured in years), household socioeconomic status (SES) and household dietary consumption were used in analyses. Household SES was measured using total wealth, a locally-developed sum of 23 traditional and modern capital measured by value in the local currency (bolivianos, Bs) that reflects economic standing (Leonard et al. 2015). Interviews in participants' homes were used to characterize dietary intake for certain foods for one week, including traditional foods (plantain and manioc (*yuca*)) or processed, market-based food (sugar), measured in kilograms (kg) (Leonard et al. 2015).

Statistical analyses

Enamel defect measures in the study sample were summarized and malnutrition-related childhood exposures were described by occurrence and extent of the enamel defects. To test whether the early childhood exposures described above were associated with enamel defects, we evaluated the relationship between each of the malnutrition-related childhood exposures and (a) enamel defect occurrence and (b) extent of enamel defects. To estimate the prevalence ratio of occurrence of enamel defects associated with each childhood exposure measured, we used log-binomial regression with robust standard errors (Deddens and Petersen 2004). To estimate the odds ratio for extent of enamel defects corresponding to each early childhood experience, we used multinomial logistic regression.

We adjusted for child age and sex at the time of the childhood exposure measurement in all analyses as potential confounders. Confidence intervals were calculated based on the standard error of the point estimates and p-values are reported. Analyses were completed using PROC TTEST, PROC MEANS, PROC FREQ, PROC GLM, PROC LOGISTIC and PROC GENMOD functions in SAS Version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

The most prevalent enamel defect pattern in the study sample was characterized by a cobblestone-like depressed surface of deficient enamel thickness on the labial surface of the central maxillary incisors, which is the focus of this analysis (prevalence = 92.3%; Figure 1). Most (44%) participants with enamel defects had 1/3 to 2/3 of the tooth surface affected, and the remainder were evenly split between <1/3 and >2/3 of the tooth surface affected (Table 1). Age at enamel assessment in adolescence was not associated with occurrence or extent of enamel defect.

Overall, 52% of participants were male. Participants were on average 3 years old at the time of the prospectively collected HAZ and WAZ measurement (Table 1). Participants, aged 1 through 4 years, had a high prevalence of stunted linear growth (75.2%), anemia (56.9%), acute inflammation (39.1%), and gastrointestinal hookworm infection (49.6%). Average Hb (p=0.35), CRP (p=0.31) or hookworm prevalence (p=0.92) did not differ greatly between males and females (Table 1).

Prospectively-collected childhood characteristics of the study population: The average HAZ was approximately -2.2 for each year of age between 1 and 4 years, indicating the average child's growth was stunted throughout early childhood years. The average WAZ increased from -1.4 at 1 year of age to -0.9 at 4 years. According to World Health Organization (WHO) cut-offs for prevalence of public health significance (and beyond the 2.3% expected prevalence), the Tsimane' had a "very high" prevalence of stunting in all ages 1-4 years and a "medium" prevalence of underweight among 1-year-old children. The prevalence of underweight in 2-4 years olds was considered "low" (Table 2) (WHO 2006). On average, the study sample did not make any relative height gains but their relative weight improved during early childhood. The prevalence of anemia was high, between 52% and 74%. Similarly, there was a high prevalence of elevated CRP, indicating possibility of acute

inflammation. The prevalence of gastrointestinal hookworm infection also increased with age from 1 to 4 years, from 11% to nearly 70%, a statistically meaningful difference (chi square, $p=0.01$).

On average, those with enamel defects had lower SES ($p=0.25$), lower household consumption of sugar ($p=0.75$) and greater household consumption of plantains ($p=0.16$) and manioc ($p=0.14$). Those with enamel defects also had a greater prevalence of stunting ($p=0.18$), anemia ($p=0.42$), acute inflammation ($p=0.55$) and hookworm gastrointestinal infection ($p=0.71$) than those without enamel defects. Mean HAZ ($p=0.04$) and mean CRP ($p<0.01$) differed significantly between those with and without enamel defects. Occurrence and extent of enamel defects did not differ by sex ($p=0.15$ and $p=0.29$, respectively) (Table 3).

Our multivariate results indicate that childhood HAZ and hookworm infection are associated with enamel defects (Table 4). For a one standard deviation (SD) increase in childhood HAZ, the prevalence of enamel defects decreased by 2% (95% CI: 0.95, 1.00; $p=0.053$). Greater linear growth was associated with decreased odds of having defective enamel on more than 2/3 of the tooth surface compared to having no defects (OR=0.65, 95% CI: 0.44, 0.96; $p=0.028$). Gastrointestinal hookworm infection increased the odds of having defective enamel on more than 2/3 of the tooth surface compared to having no defects or defects to a minimal extent (OR=3.43, 95% CI: 1.09, 10.78; $p=0.035$).

DISCUSSION

The current study provided evidence in support of associations of early childhood chronic malnutrition (HAZ) and parasitic infection (helminth infection) with a cobblestone-like depressed surface of deficient enamel thickness on the labial surface of the central maxillary incisors. These associations suggest the enamel defects are at least in part developmental in nature, having been caused between 1 and 5 years of age, when the teeth were in the alveolus and thus not exposed to the oral cavity. While HAZ may be associated with enamel defects due to common causes, it is possible that parasitic infection is a contributing direct cause of the defects if they are developmental in origin. If the cause of the observed defect pattern occurred during early life, it is possible the defect is a novel form of EH given it does not neatly fit within the typical descriptions of known EH subtypes, such as horizontal grooves, pits or missing enamel in the tooth surface (Hillson 2014).

This study is unique among the existing human population literature on enamel defects, because it prospectively recorded several early childhood (1–4 years) exposures beyond stunted growth and had the minimum follow-up time necessary (to full eruption of the permanent central maxillary incisors, at approximately 10 years of age) to evaluate these childhood exposures in relation to developmental enamel defects in the permanent dentition. There is evidence in the existing literature that childhood growth stunting and developmental enamel defects are related, and that early childhood infection and micronutrient deficiencies are possible causal mechanisms for developmental enamel defects in the permanent dentition (Sarnat and Schour 1941; Pindborg 1982; Goodman and Rose 1990; Goodman et al. 1991; Rugg-Gunn et al. 1997; Zhou and Corruccini 1998; Santos and Coimbra 1999;

Psoter et al. 2005). We thus expected to observe an inverse association of HAZ, WAZ, and Hb with developmental enamel defects, and, a positive association of CRP and hookworm infection with developmental enamel defects. Our study findings were in line with the existing literature, suggesting that developmental enamel defects are associated with stunted growth and parasitic infection. Despite the associations with early life stressors, age at enamel assessment in adolescence and occurrence or extent of enamel defects were not associated, suggesting our study sample was not biased by early mortality.

The associations observed between malnutrition-related childhood exposures and this enamel defect pattern is suggestive of the defects having developmental origins. However, the enamel defect pattern observed is characterized by an unusual cobblestone-like appearance and non-linear aspect at the margin of the lesion. The cobblestone aspect may be poorly developed or mineralized enamel, but it also could be calcified dental plaque or tartar in the area of deficient enamel. The non-linear aspect at the margin of the lesion may be the edge of a large hypoplastic depression, but we cannot rule out the possibility that post-eruptive dental erosion on susceptible areas of poorly developed enamel had also occurred, which may also be a driver of dental caries (Psoter et al. 2005; Taji and Seow 2010; Caufield et al. 2012). The enamel defect pattern observed in this study sample shares characteristics with the “plane-form” EH documented in apes and other primates, described as a “roughly circular area of deficient enamel on the labial surface” but microscopic imaging would be required to better characterize and understand the observed defect (Lukacs and Walimbe 1998; Lukacs 1999; Lukacs 2001; Skinner and Newell 2003).

Developmental enamel defects have a complex etiology with multiple pathways (Mellanby 1927; Sarnat and Schour 1941; Pindborg 1982; Goodman and Rose 1990; Seow 1991; Laskaris 2003; Golkari 2009). It is therefore possible that the primary pathway leading to enamel defects in this study sample was not captured in our childhood measures, such as inflammation of the primary central maxillary incisor root tips (“Turner’s tooth”) or fenestration of the dental crypt by physical pressure (Skinner et al. 2014). It is also likely that multiple interconnected factors, such as infection, poor growth and crypt fenestration, are on the causal pathway leading to the enamel defects we observed. Depending on the cause of the observed defect pattern, the measure of defect ‘extent’ could reflect size of fenestration or degree of exposure (if chronic in nature, may reflect a sustained or episodic nature). Unmeasured causes may explain, in part, the small proportion of enamel defects explained by the exposure variables we evaluated. Also, measurement error in enamel defects that classified those truly with enamel defects as having no enamel defects may have attenuated the point estimates in these analyses. Finally, it is also possible, given the high prevalence of enamel defects and limited sample size, the analysis lacked the statistical power to detect a significant relationship between childhood exposures and enamel defects.

Upstream factors that were presumed to have a meaningful influence on malnutrition-related exposures during early childhood were excluded from our primary analyses. These upstream factors included SES and household diet. In posthoc analyses, we investigated the potential influence of these upstream factors. The statistical relationships observed between growth stunting and hookworm infection with occurrence and extent of enamel defects were not changed when adjusted for household SES and household dietary consumption.

It was not feasible for study participants to brush their teeth prior to taking the intraoral photographs, making detection and measurement of the occurrence and extent of enamel defects less precise (due to dental plaque on the tooth surface), possibly resulting in misclassification of those truly with enamel defects as having no enamel defects. On the other hand, calcified dental plaque or tartar may have been misinterpreted as enamel defects. It may also be that the cobblestone-like depressed surface of deficient enamel thickness pattern prevalent in the Tsimane' dentition made it unlikely to detect known types of EH (i.e., linear/horizontal groove) that would otherwise been expected from acute childhood exposures (i.e., episodes of low WAZ and bouts of infectious illness). Finally, children who were missing both central maxillary incisors in adolescence and thus excluded from these analyses were taller and heavier as children. Taller and heavier children were less likely to have been exposed to childhood undernutrition and infection and less likely to have enamel defects, so the reported point estimates for childhood exposures and enamel defects may be conservative due to their exclusion. Our findings should not be generalized to populations outside Amerindian populations living in the Amazonian Basin and in the midst of a dietary and lifestyle transition like the Tsimane'.

The established associations between childhood malnutrition, enamel defects and dental caries, combined with the rising dental caries prevalence globally, emphasizes the potential importance of enamel defects as an underexplored risk factor for dental caries in certain populations (Psoter et al. 2005; Bagramian et al. 2009; Caufield et al. 2012). Additionally, teeth have the potential to serve as a permanent record, or biomarker, of early life exposures. However, as demonstrated by this study, measurement of enamel defects and ability to differentiate between post-eruptive lesions and defects of developmental origin in living human subjects, must be improved and standardized across studies. As supported by the developmental origins of health and disease framework, early life includes critical periods of development that are important targets for interventions aimed at improving oral and general health outcomes. Development of teeth as a biomarker of early life exposures may provide guidance for such interventions.

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Figure 1.

Table 1

Description of childhood demographics and malnutrition-related measures, overall

MEASURE	Overall (n=327)
	%, n or mean $\pm$ SD
Enamel defect occurrence, % yes	92.3%
Enamel defect extent	
none	7.6%
<1/3	23.6%
1/3–2/3	44.0%
>2/3	24.8%
sex, % male	52.0%
age, in years	2.8 $\pm$ 0.6
household wealth (Bs) *	3,425 $\pm$ 2,344
household diet (kg/week)	
sugar	1.5 $\pm$ 1.0
plantain	49.7 $\pm$ 22.4
manioc	10.5 $\pm$ 9.1
height-for-age z-score	–2.2 $\pm$ 1.3
% stunted (< –2.0)	75.2%
weight-for-age z-score	–1.0 $\pm$ 0.7
% underweight (< –2.0)	17.5%
hemoglobin ^f (g/dL)	10.8 $\pm$ 1.4
% with anemia	56.9%
C-reactive protein ^f (mg/L) **	1.24 (3.66)
% acute inflammation	39.1%
hookworm infection ^f	49.6%

* sum of 23 animal, trade and modern capital, measured by value in the local currency (Bs, bolivianos)

** median (interquartile range (IQR)) reported for CRP because right-skewed distribution

^f hemoglobin n=72, C-reactive protein n=64, hookworm infection n=11

Table 2

Description of malnutrition-related early childhood experiences, by year of age

MEASURE	n	1 year (n=187)	2 years (n=245)	3 years (n=269)	4 years (n=305)	Overall
height-for-age (z-score), mean $\pm$ SD	327	-2.2 $\pm$ 1.9	-2.3 $\pm$ 1.3	-2.2 $\pm$ 1.2	-2.2 $\pm$ 1.1	-2.2 $\pm$ 1.3
% stunted (< -2.0)		60.4%	61.2%	59.9%	55.1%	74.6%
weight-for-age (z-score), mean $\pm$ SD	327	-1.4 $\pm$ 0.8	-1.1 $\pm$ 0.8	-0.9 $\pm$ 0.7	-0.9 $\pm$ 0.7	-1.0 $\pm$ 0.7
% underweight (< -2.0)		21.5%	10.7%	4.1%	3.3%	17.2%
hemoglobin (g/dL), mean $\pm$ SD	72	--	10.8 $\pm$ 1.0	10.7 $\pm$ 1.5	10.7 $\pm$ 1.6	10.8 $\pm$ 1.4
% with anemia		--	52.0%	73.5%	58.3%	59.3%
C-reactive protein (mg/L), median (IQR) *	64	--	1.06 (1.68)	0.75 (2.53)	1.30 (4.54)	0.94 (3.26)
% acute inflammation		--	21.4%	29.0%	36.8%	37.0%
hookworm infection , %	113	11.1%	47.2%	42.9%	68.6%	49.6%

* median (interquartile range (IQR)) reported for CRP because right-skewed distribution

Table 3

Description of childhood demographics and malnutrition-related measures, by EH measures

MEASURE	no enamel defects (n=25)	Enamel defect occur: (n=302)	Enamel defect Extent		
			< 1/3 (n=77)	1/3 – 2/3 (n=144)	> 2/3 (n=81)
	% or mean $\pm$ SD	% or mean $\pm$ SD	% or mean $\pm$ SD	% or mean $\pm$ SD	% or mean $\pm$ SD
sex, % male	36.0%	53.5%	48.1%	56.9%	51.9%
age, in years	2.9 $\pm$ 0.5	2.8 $\pm$ 0.6	2.8 $\pm$ 0.6	2.8 $\pm$ 0.5	2.9 $\pm$ 0.7
household wealth (Bs)	3,957 $\pm$ 2,852	3,388 $\pm$ 2,308	3,634 $\pm$ 2,899	3,280 $\pm$ 2,144	3,327 $\pm$ 1,948
household diet (kg/week)					
sugar	1.5 $\pm$ 1.0	1.4 $\pm$ 1.0	1.7 $\pm$ 1.0	1.4 $\pm$ 0.9	1.2 $\pm$ 1.0
plantain	43.7 $\pm$ 16.4	49.8 $\pm$ 21.1	47.4 $\pm$ 18.3	49.9 $\pm$ 21.1	51.9 $\pm$ 23.3
manioc	8.0 $\pm$ 6.5	10.7 $\pm$ 9.1	10.1 $\pm$ 9.8	10.8 $\pm$ 9.0	11.1 $\pm$ 8.7
height-for-age z-score	-1.8 $\pm$ 1.2	-2.3 $\pm$ 1.3	-2.3 $\pm$ 1.5	-2.2 $\pm$ 1.0	-2.4 $\pm$ 1.4
% stunted (< -2.0)	64.0%	76.2%	73.7%	73.6%	82.7%
weight-for-age z-score	-1.0 $\pm$ 0.8	-1.0 $\pm$ 0.7	-1.0 $\pm$ 0.8	-1.0 $\pm$ 0.6	-1.1 $\pm$ 0.7
% underweight (< -2.0)	16.0%	17.9%	22.1%	13.4%	21.0%
hemoglobin f (g/dL)	10.9 $\pm$ 1.2	10.7 $\pm$ 1.5	10.5 $\pm$ 1.9	10.7 $\pm$ 1.4	10.8 $\pm$ 1.3
% with anemia	44.6%	55.4%	62.5%	51.7%	55.0%
C-reactive protein f (mg/L) *	1.29 (1.30)	1.24 (4.18)	1.79 (4.33)	1.24 (4.24)	0.90 (2.74)
% chronic inflammation	28.6%	40.4%	58.3%	40.0%	30.0%
hookworm infection f	42.9%	50.0%	48.0%	43.1%	63.3%

 f hemoglobin n=72, C-reactive protein n=64, hookworm infection n=113

* median (interquartile range) reported for CRP because right-skewed distribution

Early childhood experience and enamel defect regression results (prevalence or odds ratios and 95% CIs reported) ^f

	Enamel defect occurrence	Enamel defect extent		
		no defect (ref.)	< 1/3 odds ratio or (ref.)	1/3–2/3 odds ratio
height (z-score) n=327	0.98 (0.96, 1.00)	--	0.68 (0.46, 1.01)	0.72 (0.50, 1.05) 0.65* (0.44, 0.96)
weight (z-score) n=327	0.99 (0.95, 1.04)	--	0.91 (0.48, 1.72)	1.06 (0.58, 1.95) 0.76 (0.40, 1.43)
hemoglobin (g/dL) n=72	0.99 (0.95, 1.03)	--	-- ^H	1.01 (0.69, 1.47) 1.04 (0.68, 1.58)
c-reactive protein (mg/L) n=64	1.03 (0.97, 1.10)	--	-- ^H	0.96 (0.61, 1.53) 0.91 (0.55, 1.51)
hookworm infection (v. not) n=113	1.01 (0.92, 1.10)	--	-- ^H	1.07 (0.41, 2.75) 3.43* (1.09, 10.78)

^f adjusted for childhood age and sex^H due to small sample size, the “no defect” and “< 1/3” categories combined is the reference groupp<0.10 indicated in **bold font**, ***asterisk** indicates p<0.05