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Determinants of Anemia and Hemoglobin Concentration in Haitian School-Aged Children

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Abstract. Anemia diminishes oxygen transport in the body, resulting in potentially irreversible growth and developmental consequences for children. Limited evidence for determinants of anemia exists for school-aged children. We conducted a cluster randomized controlled trial in Haiti from 2012 to 2013 to test the efficacy of a fortified school snack. Children ($N = 1,047$) aged 3–13 years were followed longitudinally at three time points for hemoglobin (Hb) concentrations, anthropometry, and bioelectrical impedance measures. Dietary intakes, infectious disease morbidities, and socioeconomic and demographic factors were collected at baseline and endline. Longitudinal regression modeling with generalized least squares and logit models with random effects identified anemia risk factors beyond the intervention effect. At baseline, 70.6% of children were anemic and 2.6% were severely anemic. Stunting increased the odds of developing anemia (adjusted odds ratio [OR]: 1.48, 95% confidence interval [CI]: 1.05–2.08) and severe anemia (adjusted OR: 2.47, 95% CI: 1.30–4.71). Parent-reported vitamin A supplementation and deworming were positively associated with Hb concentrations, whereas fever and poultry ownership showed a negative relationship with Hb concentration and increased odds of severe anemia, respectively. Further research should explore the full spectrum of anemia etiologies in school children, including genetic causes.

INTRODUCTION

The hemoglobin (Hb) protein plays a fundamental role in health and development as the primary oxygen carrier in the human body. Anemia results when Hb falls below necessary levels to sustain cellular respiration and other vital processes. The World Health Organization (WHO) estimates that nearly half (48.8%) of the world's population is anemic, with notable disparities by region and population group.[1] Globally, school-aged children have a reported prevalence of 25.4%, below estimates of prevalence for preschool-aged children, pregnant, and nonpregnant women. Comparable rates have been found by various studies in low-income populations, but with relatively less evidence for this age group compared with other vulnerable groups.[2–6]

It is widely recognized that there are multiple causes of anemia, although the proportional representation of these various risk factors is less well characterized.[7] Differences across populations are further complicated by environmental and demographic factors. A recent study of children aged 6–35 months in Nyanza Province, Kenya, identified malaria, iron deficiency, and homozygous α-thalassemia as risk factors most associated with anemia; malaria, inflammation, and stunting were associated with severe anemia.[8] Another cross-sectional study in Côte d'Ivoire showed chronic inflammation and cellular iron deficiency to be associated with anemia in children aged 6–8 years, while *Plasmodium falciparum* was associated with anemia in infants aged 6–23 months, and cellular iron and riboflavin deficiencies in nonpregnant women aged 15–25 years.[6] We hypothesized a spectrum of potential causes for this population by drawing on evidence from various sources and identified factors that could be playing a role in Haiti (Figure 1).

From 2012 to 2013, we conducted a cluster randomized controlled study in Cap Haitien, Haiti, to study the impacts of a fortified peanut butter paste, Mamba, on the nutrition of school-aged children.[9] At the start of the study, anemia was found to be highly prevalent (73.3%) across all children. Although a small, positive effect was found for reduced odds of developing anemia among children receiving the Mamba nutrition intervention compared with the control (adjusted odds ratio [OR]: 0.72, 95% confidence interval [CI]: 0.57–0.91, $P < 0.001$), there were no evident differences by group for increased Hb concentration or for overall reduced anemia prevalence.[9] These findings raised questions regarding other potential causes of anemia among Haitian school-aged children. In this analysis, we aimed to investigate the observed determinants of Hb concentration, anemia, and severe anemia collected from the intervention trial, in recognition of the limitations presented by applying proxy markers, but with the intent to use the findings as a basis for further study.

METHODS

Study schools, sample, and design. The cluster randomized controlled trial was carried out in Cap Haitien, the second largest city in Haiti located in the North Department. Approximately 1 million people live in Cap Haitien and the surrounding peri-urban areas. In collaboration with the national school feeding program of the Ministry of Education (Program National de Cantine Scholaire, Ministère de l'Education Nationale et de la Formation Professionnelle), formative research was carried out to identify and match schools on socioeconomic and nutrition factors. Six comparable schools were selected, including four public and two private schools, and randomized into three groups: control, cereal bar (Tablet Yo), and fortified peanut butter snack (Mamba). Details of the trial are described elsewhere.[9]

In brief, children were considered eligible based on the following criteria: aged 3–13 years; good health (no fever, congenital health condition, or peanut or soy allergy); not severely malnourished (weight-for-height z score [WHZ] < −3); and registration in study school for 2012–2013. Of the 1,169 eligible children, 1,167 were enrolled; for this analysis, we included

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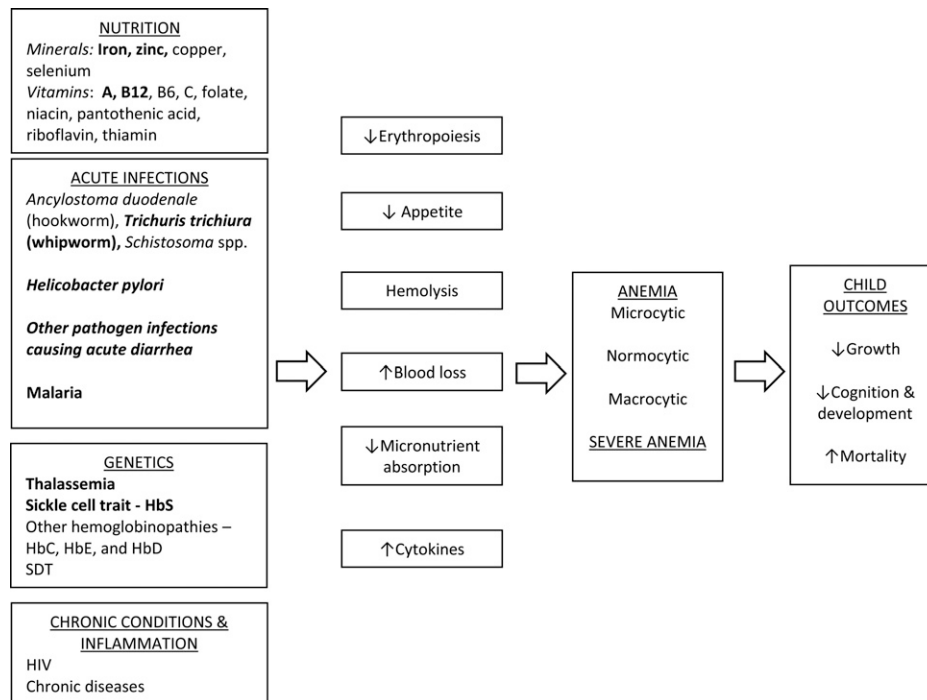
FIGURE 1. Potential causal pathways for determinants of anemia in school-aged children. The determinants in boldface are those hypothesized to be contributing to anemia among school-aged children in Cap Haitien, Haiti.

the children with Hb concentration measures at two or more time points ($N = 1,047$). In this analysis, we refer to the sample as school-aged children, though 182 preschool-aged children were included. Children were followed longitudinally for Hb concentration, height, weight, and bioelectrical impedance measures at three time points: baseline (December 2012), midline (March 2013), and endline (June 2013). Parents were surveyed for household level socioeconomic, demographic factors and water, hygiene, and sanitation information, as well as child diet and morbidities at baseline and endline. In addition to household income, we assessed ownership of various assets, including livestock (cows, donkeys, goats, and poultry).

Children in the two intervention groups received the snack daily from January through June 2013. Mamba (50 g, 260 kcal) provided greater than 75% of Recommended Dietary Allowances (RDA) for critical micronutrients (vitamin A, B_{12}, folate, copper, iron, selenium, and zinc) for children aged 4–8 years including those associated with anemia.[10] The Tablet Yo cereal bar (42 g, 165 kcal) offered these nutrients at lower levels ranging from 0% to 62% of RDA. Children in the control group did not receive any snack during the study period. The study was approved by the National Bioethics Committee of the Ministry of Health (Ministère de la Santé Publique et de la Population, MSPP) in Haiti and the Institutional Review Board of the Human Research Protection Office of Washington University in St. Louis.

Hb and anemia. Hb concentration and nutrition markers were collected at three time points using standardized protocols. Enumerators were trained in the month before baseline data collection and received a refresher training 2 weeks before endline data collection period. For Hb, blood was collected using a finger stick to the middle finger of the right hand in each child and transferred to microcuvette in one continuous process. The microcuvette was then inserted into a HemoCue Hemoglobin 201+ Analyzer (HemoCue AB, Angelholm, Sweden) to determine the Hb concentration, reported in grams per deciliter (g/dL). The HemoCue System has been validated against standard laboratory techniques for measurement of Hb concentration in normal and in anemic children, with and without Hb disorders.[11]

Results were compared with WHO anemia and severe anemia thresholds.[12] Anemia thresholds applied for the school-age children were the following: < 5 years (anemia 11.0 g/dL, severe anemia 7.0 g/dL); 5–11 years (anemia 11.5 g/dL, severe anemia 8.0 g/dL); and 12–14 years (anemia 12.0 g/dL, severe anemia 8.0 g/dL). Minimal evidence exists for appropriate adjustment levels for race. Estimates for lower Hb threshold for African–Americans in the United States range from 0.5 to 1.0 g/dL.[13–15] Given the limited evidence supporting adjustment by race in global research contexts, WHO does not recommend adjustment; we thus applied the WHO thresholds for all analyses. No adjustment for altitude was necessary because Cap Haitien is less than 1,000 m above sea level.

Nutrition and health. Child anthropometric measures of weight and height were taken using international protocols.[16] Weight was measured to the nearest 0.1 kg using the digital Seca Model 874 (Seca North America, Chico, CA) and height to the nearest 1 mm with the ShorrBoard (Weigh and Measure, LLC, Olney, MD). Body mass index (BMI), anthropometric z scores, and prevalence of stunting (height-for-age z score [HAZ] < −2), underweight (weight-for-age z score [WAZ] < −2), wasting (WHZ < −2), and thin (BMI z score [BMIz] < −2) were calculated based on WHO Growth Standards (2006) for children aged 3–5 years, and WHO Growth References (2007) for children aged 6–13 years.[17,18]

Caregiver surveys, administered at baseline and endline, were used to collect information regarding child diet, supplementation, deworming, and morbidities. Caregivers were asked

whether the child had received vitamin A, iron, zinc, multi-vitamins, mineral supplements, or deworming tablets in the previous 6 months. Child diet was examined using a 24-hour food frequency of intake. Enumerators asked caregivers to recall the number of times the child had consumed various foods in the past day and night. Two indicators were generated to examine micronutrient nutrition and dietary quality: dietary diversity and animal source food (ASF) consumption. Dietary diversity was calculated by summing the number of food items consumed in 24-hour period.[19] The ASF indicator was a dichotomous marker of whether the child had consumed any eggs, milk, meat, or fish in the past day and night.

Child morbidity outcomes were similarly assessed using a caregiver recall. Enumerators asked if the child had experienced the following diarrheal morbidities in the past 2-week period: acute diarrhea (three or more semisolid or liquid stools in a 24-hour period), number of days with acute diarrhea, and bloody diarrhea. A 1-month recall period was applied for all other morbidities: malaria, fever, respiratory condition (cough and short, rapid breathing), eye infection, ear infection, skin conditions, and worm infection. All morbidity variables were assessed in the regression models.

Statistical analysis. All statistical analyses were carried out using STATA software (version 13.1; StataCorp, College Station, TX). To begin, descriptive statistics were applied to characterize anemia prevalence and distributions among the school-age children. Next, univariate tests of analysis of variation, t tests, and χ^2 examined differences in socioeconomic, demographic, nutrition, and morbidity outcomes by anemia and severe anemia status. We investigated Hb concentrations, distributions, and anemia status differences by child age. Age across the range of children included in this study (3–13 years) was stratified according to common groupings in the nutrition and anemia literature: preschool-aged (2–5 years), school-aged (6–8 and 9–11 years), and preadolescence (12–13 years) children. Values for continuous outcomes are given as means ± standard deviation, except for coefficient values in regression models presented as means ± standard error of the estimate.

Longitudinal models were then constructed to identify determinants of Hb concentration, anemia, and severe anemia. Generalized least squares (GLS) with random effects was applied for the continuous outcome of Hb concentration, and logit models examined the adjusted odds for the dichotomous anemia and severe anemia outcomes.[20] We applied a Bayesian approach to constructing and interpreting the models.[21] Variables representing conditions in the hypothesized causal pathways to anemia were first tested in the models (Figure 1). We included those related to nutrition (anthropometry, diet, and micronutrient supplementation), infection (all parent-recall morbidities including diarrhea, malaria, fever, and helminth infection), and chronic infection or conditions (child allergies, family history of chronic diseases). After this, the full set of available socioeconomic, demographic, nutrition, and health factors were incorporated into models as independent variables. Models including the variables collected at baseline and endline compared change in outcomes at two time points only. Those found to be significant ($P < 0.05$) and not highly correlated with other terms ($r \leq 0.7$) were retained. Separate models were run for each age group strata to test whether there were differences in the determinants of Hb concentration and anemia outcomes. All models were adjusted for treatment group and school cluster.

RESULTS

Socioeconomic, demographic, and health characteristics. Baseline characteristics were not statistically different by anemia status, except for prevalence of acute diarrhea in the previous 2 weeks (Table 1). Trends for differences were observed for stunting and poultry ownership. Across all children, a greater proportion of children were reported receiving vitamin A supplementation (19.8%) in the previous 6 months compared with iron supplementation (8.9%). At baseline, the proportion of children receiving vitamin A supplements did not differ significantly by age: 2–5 years (22.4%), 6–8 years (21.6%), 9–11 years (17.0%), and 12–13 years (17.0%) ($P = 0.28$). Fever in the past 2 weeks was reported in 23.8% of all children; a greater, non-significant proportion was found in the anemia group. Across all children, 65.8% of households were in the lowest income quartile, and use of latrine and open defecation were the most common sanitation practices.

Hb concentrations and anemia prevalence and trends. Mean Hb concentrations were statistically different by age group, with preschool-aged children showing the lowest levels (Table 2). Similarly, prevalence of anemia was also statistically different by age group. No statistical differences in Hb or anemia by sex were evident. With the exception of the age group 9–11 years, Hb concentration was lower at endline compared with baseline; anemia prevalence increased only in the youngest group. Severe anemia increased from baseline to endline across all age groups, again except in the 9- to 11-year olds. At the individual child level, 18.8% became anemic from baseline to endline, while 15.6% recovered, 65.6% did not move across categories. For severe anemia, 2.3% of the children fell into this category by endline and 2.8% recovered.

Longitudinal regression modeling. Longitudinal modeling of Hb concentration showed that age of the child, vitamin A supplementation, and deworming were associated with positive change in Hb, while stunting and fever negatively affected change in Hb concentration for individual children (Table 3). Malaria morbidity was found to significantly increase the odds of anemia, but because it was positively correlated with fever morbidity and explained overlapping variance in the anemia outcomes with fever, it was not retained in the model. A positive trend for consumption of ASFs was evident in association with changes in Hb concentration and for protecting against severe anemia. Stunting increased the odds of anemia by 48% and severe anemia by 147%. Increasing age of the child reduced the odds of anemia but was not associated with severe anemia outcomes. Girls were at greater risk for severe anemia. Children whose parents reported owning poultry were at increased odds of severe anemia. In the substrata analyses by age group, trends suggested comparable determinants of Hb concentration and anemia outcomes to the larger sample.

DISCUSSION

The prevalence of anemia among these Haitian children was 70.6% at trial baseline. This longitudinal, cohort study offers epidemiological evidence for determinants of anemia as a foundation for future research in an understudied age demographic and context. Stunting was strongly and consistently related to change in Hb concentration, anemia, and severe anemia outcomes in these children. Other nutrition factors played a role, including vitamin A supplementation

	Controls (nonanemic children, N = 309)		Cases (anemic children, N = 738)		
	Mean or %	SD	Mean or %	SD	P value
Child characteristics					
Child age, years*	8.0	2.5	8.2	2.5	0.26
Sex of child, % female	51.5	–	51.6	–	0.96
Undernutrition, %					
Stunted (HAZ < −2)	11.1		15.0		0.13
Thin (BMIz < −2)	9.5		9.0		0.82
ASFs consumption, %	50.2	–	53.3	–	0.35
Supplementation in previous 6 months, %					
Vitamin A	21.3		18.9		0.38
Iron	9.5		9.0		0.81
Deworming in previous 6 months, %	78.4	–	75.7	–	0.35
Acute diarrhea, %†	15.6	–	11.0	–	0.04
Fever, %	21.6	–	25.1	–	0.23
Caregiver characteristics					
Maternal education, years*	4.5	3.5	4.5	3.5	0.98
Maternal BMI (N = 945)*	23.2	4.8	23.3	4.6	0.93
Household characteristics					
Total number of household members*	6.4	2.4	6.4	2.7	0.64
Sol savings club participation, %	68.6		67.4		0.77
Monthly income (Haitian dollar), %					0.71
100–500	65.0		66.4		
501–800	13.4		14.5		
801–1,000	9.8		7.5		
> 1,000	11.8		11.4		
Poultry ownership, %	10.5		14.4		0.09
Toilet type, %					0.26
Open defecation/other	20.5		18.7		
Latrine	70.7		74.9		
Automatic flush	8.8		6.4		
Share toilet with other households, %	41.0		37.9		0.34
Drinking water source, %					0.94
Public pump	8.8		9.4		
Tap or faucet inside home	25.8		25.7		
Bottled or potable water	61.8		60.6		
Other (truck, well, spring, surface)	3.6		4.4		

ASFs = animal source foods; BMIz = body mass index z score; HAZ = height-for-age z score; SD = standard deviation.
* Values are mean ± SD.
† Groups were significantly different by analysis of variance or χ^2, $P < 0.05$.

TABLE 2
Mean Hb concentration and anemia prevalence at three time points, by age group

Age group	Hb concentration (g/dL)	SD	WHO-defined anemia	Severe anemia
2–5 years (N = 182)				
Baseline	10.2	1.4	65.6	2.2
Midline	10.2	1.4	71.3	1.7
Endline	10.1	1.1	70.3	3.3
6–8 years (N = 388)				
Baseline	10.4	1.3	73.4	3.6
Midline	10.7	1.3	69.1	3.1
Endline	10.3	1.3	71.4	4.1
9–11 years (N = 365)				
Baseline	10.8	1.3	66.9	2.2
Midline	11.1	1.2	59.6	1.0
Endline	10.8	1.3	63.6	1.6
12–13 years (N = 112)				
Baseline	10.9	1.2	81.3	1.0
Midline	10.7	1.6	80.4	6.3
Endline	10.7	1.4	75.0	4.5
All (N = 1,047)				
Baselines	10.6*	1.2	70.6*	2.6
Midline	10.7*	1.4	67.3*	2.3*
Endline	10.5*	1.3	68.9*	3.2

Hb = hemoglobin; SD = standard deviation; WHO = World Health Organization.
* Age groups were significantly different by analysis of variance or χ^2, $P < 0.05$.

and dietary intake of ASFs. Markers of infection (fever and deworming) and potential pathogen exposure (poultry ownership) were associated with Hb concentration and anemia in the expected directions.

To our knowledge, anemia has not been previously evaluated in Haitian school-aged children. Evidence comes largely from children 6 to 59 months and women of reproductive age, with some parallel findings to this analysis. A recent, nationally representative study in Haiti showed urban women and children are at higher risk for anemia than those in rural areas.[22] Other contributing factors for young children included age, maternal nutritional status, and female sex. Another study from the south of Haiti showed 38.8% children aged 6–59 months were anemic, in association with young age, stunting, and low maternal Hb status.[23] A third study, applying a convenience sample and cross-sectional design in the Central Plateau of Haiti, found 80.1% of preschool-aged children to be anemic.[24] Prevalence varied by context, but similar to our findings age, stunting, and female sex were associated with increased anemia risks.

Age and sex of the child. Age was protective for Hb concentration and anemia, suggesting a need to target younger children both within and outside the school system. Girls were

TABLE 3
Longitudinal regression models for determinants of Hb concentration, anemia, and severe anemia in Haitian school children

	Hb (g/dL)* ($N = 1,684$ observations)		Anemia† ($N = 1,699$ observations)		Severe anemia† ($N = 1,699$ observations)	
	Coefficient (SEE)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age of child, years	0.11 (0.01)	< 0.001	0.94 (0.89–0.98)	0.01	–	–
Sex of child (0 = boy, 1 = girl)	–	–	–	–	1.81 (1.02–3.23)	0.04
Stunted (HAZ < −2)	−0.40 (0.09)	< 0.001	1.48 (1.05–2.08)	0.03	2.47 (1.30–4.71)	0.01
Nutrition						
Vitamin A supplement in last 6 months	0.18 (0.08)	0.02	–	–	–	–
Consumed any ASFs in last 24 hours	0.12 (0.06)	0.07	–	–	0.57 (0.31–1.03)	0.06
Infection						
Deworming in last 6 months	0.17 (0.07)	0.02	–	–	–	–
Fever in last 2 weeks	−0.18 (0.08)	0.02	1.28 (0.96–1.70)	0.09	–	–
Poultry ownership	–	–	–	–	2.06 (1.02–4.15)	0.04
Overall R^2	0.07		0.02		0.07	
Wald χ^2/LR χ^2	118.71	< 0.001	26.62	0.01	34.48	0.001

ASFs = animal source foods; CI = confidence interval; HAZ = height-for-age z score; Hb = hemoglobin; OR = odds ratio; SEE = standard error of the estimate.
*Generalized least squares regression with random effects, adjusted for intervention group and school cluster.
†Logit model with random effects, adjusted for intervention group and school cluster.

at significantly greater risk for severe anemia compared with boys. In our subgroup analyses examining anemia in girls and boys, we found a trend for increased anemia among older girls, 12–13 years of age. In an older study, average age at menarche in Haiti was found to be 15.4 years, with a secular trend of declining age by 0.36 years per year.[25] Thus, it is plausible that some older girls were at greater risk for anemia because of the blood loss associated with menses.

Stunting. Stunting significantly increased the odds of anemia and severe anemia in these school-aged children. Changes in HAZ were also found to be positively associated with changes in Hb concentration and negatively related to anemia status. The relationship was strong and consistent across models, with evidence for a biological gradient in association with Hb concentration and risk for anemia and severe anemia. Shared mechanisms exist in this relationship, namely micronutrient deficiencies and infectious disease morbidities. Stunting may arise from deficiencies in zinc and vitamin A, which are also known to increase the risk of anemia through impaired erythropoiesis and oxidative stress pathways.[26–28] One large study in Shaanxi Province, China, found HAZ associated with anemia in school-aged children.[3] In Côte d'Ivoire, stunting was negatively associated with Hb concentrations and positively with anemia in school-aged children.[29]

Dietary intakes. The fortified snack, Mamba, reduced the odds of anemia by 28% compared with control for individual children.[9] Mamba contains higher levels of critical micronutrients than the cereal bar, suggesting a potential role for nutrient deficiencies in causing anemia. Our analysis supported this hypothesis by showing an association between vitamin A supplementation and ASF consumption and Hb concentration and anemia outcomes.

Parent-reported vitamin A supplementation of the child in the past 6 months was found to significantly increase Hb concentration by 0.18 g/dL after adjusting for all other covariates. In Haiti, the MSPP protocol is to provide high-dose vitamin A supplementation every 6 months for children 6 months–6 years. Although higher proportions of children in the younger age groups received vitamin A than older children, the difference was not significant. Approximately one-fifth (19.8%) of all the school children in our study were reported to have received vitamin A supplements. Evidence suggests vitamin A influences anemia primarily through mechanisms to regulate erythropoiesis and mediate iron metabolism (iron storage and release).[27]

Iron deficiency has previously been thought to comprise the largest proportion of anemia, with estimates ranging from 50% for malaria-endemic regions to 60% in other developing countries.[30] However, this has not been verified in other epidemiological studies and was not indicated in our findings. Iron supplementation, albeit only reported in 9% of the children, was not associated with anemia outcomes or Hb concentration. The Kenya study showed the fractional prevalence of iron deficiency anemia to be only 8.3% among preschool-aged children.[8] In Thailand, iron deficiency anemia was prevalent only among the preschool-aged children (19%), while there was no evidence of anemia related to iron deficiency in the school-aged children.[2] The Côte d'Ivoire analyses found an association with cellular iron deficiency and anemia in school-aged children at baseline,[6] and a negative association with Hb concentration in the prospective study.[29] Importantly, the iron parameters (ferritin and soluble transferrin receptor) were associated with inflammatory biomarkers.

Vitamin B_{12} and folate deficiencies result in macrocytic anemia, a condition in which hematopoietic stem cells in the bone marrow and red blood cells in circulation are larger than normal. This results from the asynchronous growth of cytoplasm and nucleic material.[7] One study among school-aged children in Colombia found that Hb concentration was inversely related to erythrocyte folate concentrations, in particular, among children with low vitamin B_{12} status.[31] Although we were not able to directly examine status for these nutrients, consumption of ASF as the only dietary source of vitamin B_{12} might be considered a proxy marker.[32] We found a positive trend for ASF and Hb concentrations ($P = 0.07$) and for ASF reducing the odds of severe anemia ($P = 0.06$) in longitudinal modeling. ASF consumption may also be protective for other nutrients implicated in anemia risk including vitamin A, iron, and zinc.

Acute infection. Deworming and fever showed important associations with Hb concentration in our regression analyses. A recent MSPP study on helminth infection in Haitian children 6–15 years of age found a national prevalence of 14% (95% CI: 13.1–15.0%), and a prevalence of 15.9% in the North Department where our study was conducted.[33] Interestingly, this study showed limited infection with hookworm, 0.4% (95% CI: 0.3–0.7%), a known contributor to anemia. *Trichuris trichiura* (whipworm) was prevalent in 9.0% (95% CI: 8.2–9.8%) and *Ascaris lumbricoides* in 9.2% (95% CI: 8.4–10.0%) of Haitian children, nationally. Although *T. trichiura*

is more directly related to anemia through blood losses, *A. lumbricoides* could be contributing through inflammation mechanisms.[34] One study from Leogane in southern Haiti reported infection rates between 11% and 37% for *A. lumbricoides*, between 19% and 62% for *T. trichiura*, and between 6% and 21% for hookworm.[35]

The negative relationship of fever with Hb concentration after adjusting for deworming in our analyses suggests a role for other types of infection. Malaria was the leading cause of anemia and severe anemia in the Kenya study looking at multiple etiologies.[8] However, prevalence in Haiti is estimated to be only 1–3% with variability by season and region of the country.[36,37] There was a sharp increase in cases from 2009 to 2011, but rates have dropped and stabilized since; approximately half of the population lives in high-transmission (> 1 case per 1,000 population) areas.[38] The Côte d'Ivoire studies also showed both acute and chronic inflammation markers to be associated with anemia.[6,29] Other gastrointestinal infections may be playing a role in Haiti. Though acute diarrhea was not significantly related to anemia in the school-aged children, poultry ownership, a potential exposure variable, was associated with a 2-fold higher odds of severe anemia.[39,40]

Strengths and limitations. To our knowledge, this is the first known analysis to examine the determinants of anemia among school-aged children in Haiti. Although the study was designed to test the effectiveness of a snack intervention on anemia and other nutrition outcomes, the data collected allowed for exploration of a range of hypothesized factors. There were key pathways, however, that we were not permitted to explore, such as genetics. Small studies have been carried out in Haiti that suggest the importance of the hereditary hemoglobinopathies such as sickle Hb in the anemia pathway.[41–43] Other potential mechanisms were assessed only through the use of proxy markers that lacked precision and specificity. More ideally, we would have tested for helminth and *Plasmodium* infections through methods such as the Kato-Katz or FLOTAC methods and blood films or rapid diagnostic tests, respectively.[44,45] Biomarkers of micronutrient status also may have improved precision for the distinct contributions of various vitamins and minerals.[46]

These analyses were intended to serve as a basis for further exploration of anemia etiologies in Haiti and elsewhere. Findings clearly suggest a very high prevalence of anemia in Haiti using the WHO cutoff. As a longitudinal study, we were able to examine drivers of change in Hb concentration and anemia status through the use of powerful regression models. Stunting, which could indicate micronutrient deficiencies as well as infection, was strongly associated with all Hb concentration, anemia, and severe anemia outcomes. Other nutrition factors identified, including vitamin A supplementation and ASF dietary intakes, are suggestive of an important role for micronutrient deficiencies in Haiti. There was also clear evidence for infection-related determinants.

CONCLUSIONS

Anemia encompasses several different conditions, unified by the definition of low Hb concentration. The etiological range may reflect the vital importance of the Hb protein as oxygen carrier, and similarly, multiple mechanisms that can compensate when deficits arise. Although anemia is commonly examined as the outcome of interest, we want to emphasize that it is a condition that can lead to serious and possibly irreparable impairments in growth, development, and reproductive health. For school-aged children undergoing rapid brain development and underlying physiological processes of growth and development, the consequences may be severe. Moving forward, research is still needed to understand the full range of causes of anemia using valid markers of potential risk factors, and to test interventions related to nutrition and infection to reduce this problem in Haiti and elsewhere.

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REFERENCES

1. de Benoist B, McLean E, Egli I, Cogswell M, 2008. *Worldwide Prevalence of Anaemia 1993–2005*. Geneva, Switzerland: World Health Organization.
2. Linpisarn S, Tienboon P, Promtet N, Putsyainunt P, Santawanpat S, Fuchs JG, 1996. Iron deficiency and anaemia in children with a high prevalence of haemoglobinopathies: implications for screening. *Int J Epidemiol 25:* 1262–1266.
3. Luo R, Kleiman-Weiner M, Rozelle S, Zhang L, Liu C, Sharbono B, Shi Y, Yue A, Martorell R, Lee M, 2010. Anemia in rural China's elementary schools: prevalence and correlates in Shaanxi Province's poor counties. *Ecol Food Nutr 49:* 357–372.
4. Luo R, Zhang L, Liu C, Zhao Q, Shi Y, Miller G, Yu E, Sharbono B, Medina A, Rozelle S, Martorell R, 2011. Anaemia among students of rural China's elementary schools: prevalence and correlates in Ningxia and Qinghai's poor counties. *J Health Popul Nutr 29:* 471–485.
5. Best C, Neufingerl N, Del Rosso JM, Transler C, van den Briel T, Osendarp S, 2011. Can multi-micronutrient food fortification improve the micronutrient status, growth, health, and cognition of schoolchildren? A systematic review. *Nutr Rev 69:* 186–204.
6. Righetti AA, Koua AYG, Adiossan LG, Glinz D, Hurrell RF, N'Goran EK, Niamké S, Wegmüller R, Utzinger J, 2012. Etiology of anemia among infants, school-aged children, and young non-pregnant women in different settings of south-central Côte d'Ivoire. *Am J Trop Med Hyg 87:* 425–434.
7. Hoffbrand A, Moss P, Pettit J, 2006. *Essential Haematology*. Oxford, United Kingdom: Blackwell Publishing.
8. Foote EM, Sullivan KM, Ruth LJ, Oremo J, Sadumah I, Williams TN, Suchdev PS, 2013. Determinants of anemia among preschool children in rural, western Kenya. *Am J Trop Med Hyg 88:* 757–764.

9. Iannotti L, Henretty N, Delnatus J, Previl W, Stehl T, Vorkoper S, Bodden J, Maust A, Smidt R, Nash MCT, Owen B, Wolff P, 2015. Ready-to-use supplementary food increases fat mass and BMI in Haitian school-age children. *J Nutr 145:* 813–822.

10. IOM, 2014. *Dietary Reference Intakes (DRIs): Estimated Average Requirements.* Available at: http://www.iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/ActivityFiles/Nutrition/DRIs/5_Summary Table Tables 1-4.pdf. Accessed August 19, 2014.

11. Cohen AR, Seidl-Friedman J, 1988. HemoCue system for hemoglobin measurement. Evaluation in anemic and nonanemic children. *Am J Clin Pathol 90:* 302–305.

12. WHO, 2011. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity.* Geneva, Switzerland: World Health Organization.

13. Dallman PR, Barr GD, Allen CM, Shinefield HR, 1978. Hemoglobin concentration in white, black, and Oriental children: is there a need for separate criteria in screening for anemia? *Am J Clin Nutr 31:* 377–380.

14. Johnson-Spear MA, Yip R, 1994. Hemoglobin difference between black and white women with comparable iron status: justification for race-specific anemia criteria. *Am J Clin Nutr 60:* 117–121.

15. Robins EB, Blum S, 2007. Hematologic reference values for African American children and adolescents. *Am J Hematol 82:* 611–614.

16. Cogill B, 2003. *Anthropometric Indicators Measurement Guide.* Washington, DC: Food and Nutrition Technical Assistance Project, Academy for Educational Development.

17. WHO, 2006. *The WHO Child Growth Standards.* Available at: http://www.who.int/childgrowth/en/. Accessed October 23, 2014.

18. WHO, 2007. *Growth Reference Data for 5–19 Years.* Available at: http://www.who.int/growthref/en/. Accessed October 23, 2014.

19. Swindale A, Bilinsky P, 2006. *Household Dietary Diversity Score (HDDS) for Measurement of Household Food Access: Indicator Guide, Version 2.* Washington, DC: Food and Nutrition Technical Assistance Project, Academy for Educational Development.

20. Hedeker D, Gibbons RD, 2006. *Longitudinal Data Analysis.* Hoboken, NJ: John Wiley and Sons, Inc.

21. Rothman K, Greenland S, 1998. *Modern Epidemiology.* Philadelphia, PA: Lippincott Williams and Wilkins.

22. Heidkamp RA, Ngnie-Teta I, Ayoya MA, Stoltzfus RJ, Mamadoultaibou A, Durandisse EB, Pierre JM, 2013. Predictors of anemia among Haitian children aged 6 to 59 months and women of childbearing age and their implications for programming. *Food Nutr Bull 34:* 462–479.

23. Ayoya MA, Ngnie-Teta I, Séraphin MN, Mamadoultaibou A, Boldon E, Saint-Fleur JE, Koo L, Bernard S, 2013. Prevalence and risk factors of anemia among children 6–59 months old in Haiti. *Anemia 2013:* 1–3.

24. Shak JR, Sodikoff JB, Speckman RA, Rollin FG, Chery MP, Cole CR, Suchdev PS, 2011. Anemia and *Helicobacter pylori* seroreactivity in a rural Haitian population. *Am J Trop Med Hyg 85:* 913–918.

25. Barnes-Josiah D, Augustin A, 1995. Secular trend in the age at menarche in Haiti. *Am J Hum Biol 7:* 357–362.

26. Badham J, Zimmerman MB, Kraemer K, 2007. *The Guidebook: Nutritional Anemia.* Basel, Switzerland: Sight and Life Press.

27. Semba RD, Bloem MW, 2002. The anemia of vitamin A deficiency: epidemiology and pathogenesis. *Eur J Clin Nutr 56:* 271–281.

28. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, Ezzati M, Grantham-Mcgregor S, Katz J, Martorell R, Uauy R, 2013. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet 382:* 427–451.

29. Righetti AA, Adiossan LG, Ouattara M, Glinz D, Hurrell RF, N'Goran EK, Wegmüller R, Utzinger J, 2013. Dynamics of anemia in relation to parasitic infections, micronutrient status, and increasing age in south-central Côte d'Ivoire. *J Infect Dis 207:* 1604–1615.

30. Rastogi T, Mathers C, 2002. *Global Burden of Iron Deficiency Anaemia in the Year 2000.* Geneva, Switzerland: World Health Organization.

31. Arsenault JE, Mora-Plazas M, Forero Y, Lopez-Arana S, Baylin A, Villamor E, 2008. Hemoglobin concentration is inversely associated with erythrocyte folate concentrations in Colombian school-age children, especially among children with low vitamin B_{12} status. *Eur J Clin Nutr 63:* 842–849.

32. Mann J, Truswell S, 2012. *Essentials of Human Nutrition.* Oxford, United Kingdom: Oxford University Press.

33. MSPP, 2013. Evaluation de la prévalence des helminthiases intestinales chez les enfants de 6 à 15 ans scolarisés en Haïti, Octobre 2013. Port-au-Prince, Haiti: Ministère de la Santé Publique et de la Population.

34. Stephenson LS, Holland CV, Cooper ES, 2000. The public health significance of *Trichuris trichiura. Parasitology 121:* S73–S95.

35. de Rochars MB, Direny AN, Roberts JM, Addiss DG, Radday J, Beach MJ, Streit TG, Dardith D, Lafontant JG, Lammie PJ, 2004. Community-wide reduction in prevalence and intensity of intestinal helminths as a collateral benefit of lymphatic filariasis elimination programs. *Am J Trop Med Hyg 71:* 466–470.

36. PSI, 2011. TRaC malaria: étude TRaC sur la possession et l'utilisation des moustiquaires imprégnées d'insecticides et la prévalence du paludisme en Haiti. Port-au-Prince, Haiti: Population Services International.

37. Eisele TP, Keating J, Bennett A, Londono B, Johnson D, Lafontant C, Krogstad DJ, 2007. Prevalence of *Plasmodium falciparum* infection in rainy season, Artibonite Valley, Haiti, 2006. *Emerg Infect Dis 13:* 1494–1496.

38. WHO, 2014. *World Malaria Report 2014.* Geneva, Switzerland: World Health Organization.

39. Marquis GS, Ventura G, Gilman RH, Porras E, Miranda E, Carbajal L, Pentafiel M, 1990. Fecal contamination of shanty town toddlers in households with non-corralled poultry, Lima, Peru. *Am J Public Health 80:* 146–149.

40. Ngure FM, Humphrey JH, Mbuya MNN, Majo F, Mutasa K, Govha M, Mazarura E, Chasekwa B, Prendergast AJ, Curtis V, Boor KJ, Stoltzfus RJ, 2013. Formative research on hygiene behaviors and geophagy among infants and young children and implications of exposure to fecal bacteria. *Am J Trop Med Hyg 89:* 709–716.

41. Randolph TR, 2010. Estimated prevalence of sickle cell in northern Haiti. *Clin Lab Sci 23:* 79–83.

42. Rotz S, Arty G, Dall'Amico R, De Zen L, Zanolli F, Bodas P, 2013. Prevalence of sickle cell disease, hemoglobin S, and hemoglobin C among Haitian newborns. *Am J Hematol 88:* 827–828.

43. Carter TE, von Fricken M, Romain JR, Memnon G, St Victor Y, Schick L, Okech BA, Mulligan CJ, 2014. Detection of sickle cell hemoglobin in Haiti by genotyping and hemoglobin solubility tests. *Am J Trop Med Hyg 91:* 406–411.

44. Bell D, Peeling RW, 2006. Evaluation of rapid diagnostic tests: malaria. *Nat Rev Microbiol 4:* S34–S40.

45. Knopp S, Salim N, Schindler T, Voules DAK, Rothen J, Lweno O, Mohammed AS, Singo R, Benninghoff M, Nsojo AA, Genton B, Daubenberger C, 2014. Diagnostic accuracy of Kato-Katz, FLOTAC, Baermann, and PCR methods for the detection of light-intensity hookworm and *Strongyloides stercoralis* infections in Tanzania. *Am J Trop Med Hyg 90:* 535–545.

46. Gibson RS, 2005. *Principles of Nutrition Assessment.* New York, NY: Oxford University Press.