Anthropometry and Malaria among Children in Niger: A Cross-Sectional Study

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Abstract. The complex relationship between malnutrition and malaria affects morbidity and mortality in children younger than 5 years, particularly in parts of sub-Saharan Africa where these conditions occur together seasonally. Previous research on this relationship has been inconclusive. Here, we examine the association between anthropometric indicators and malaria infection in a population-based sample of children younger than 5 years in Niger. This cross-sectional study is a secondary analysis of a cluster-randomized trial comparing treatment strategies for trachoma in Niger. We included children aged 6–60 months residing in the 48 communities enrolled in the trial who completed anthropometric and malaria infection assessments at the final study visit. We evaluated the association between anthropometric indicators, including height-for-age z-score (HAZ) and weight-for-age z-score (WAZ) and indicators of malaria infection, including malaria parasitemia and clinical malaria. In May 2013, we collected data from 1,649 children. Of these, 780 (47.3%) were positive for malaria parasitemia and 401 (24.3%) had clinical malaria. In models of malaria parasitemia, the adjusted odds ratio (aOR) was 1.05 (95% confidence interval [CI]: 1.00–1.10) for HAZ and 1.07 (95% CI: 0.99, 1.15) for WAZ. In models of clinical malaria, the aOR was 1.07 (95% CI: 1.02–1.11) for HAZ and 1.09 (95% CI: 1.01–1.19) for WAZ. Overall, we did not find evidence of an association between most anthropometric indicators and malaria infection. Greater height may be associated with an increased risk of clinical malaria.

INTRODUCTION

Malnutrition and malaria are among the leading causes of morbidity and mortality among children, particularly in sub-Saharan Africa.¹ Undernutrition is directly or indirectly responsible for 45% of deaths among children younger than 5 years worldwide.² Although mortality from malaria has decreased in recent years, malaria caused approximately 730,000 deaths in 2015, with the burden of malaria-related mortality concentrated in children younger than 5 years.^{1,3} Sub-Saharan African countries bear the greatest burden of both conditions, having among the highest rates of malnutrition and malaria globally.^{1–3} Moreover, malaria and malnutrition tend to occur together and the complexity of this association has yet to be fully described.

The relationship between nutritional status and malaria has a major impact on morbidity and mortality among young children. Malnutrition and malaria have similar seasonality in the Sahel and sub-Sahel regions of West Africa.^{4,5} Malnutrition peaks during the “lean” season between harvests, which coincides with the rainy season, when mosquitoes breed and malaria infection increases. It has also been suggested that a biological or immunological interaction between malaria and malnutrition could exacerbate both conditions.^{6,7} Malnutrition affects the immune system, leaving malnourished children more vulnerable to infections such as malaria and impeding recovery.^{7,8} Children with malaria may also be more likely to become malnourished and the presence of infection may negatively impact response to treatment of malnutrition.

Previous studies on the relationship between malnutrition and malaria have found conflicting results.⁶ Some indicate that

malnutrition may increase the risk or severity of malaria.^{9–15} Specifically, studies have found increases in malaria risk associated with stunting,⁹ arm circumference by age,¹⁰ and underweight,¹¹ as well as associations between underweight and mortality,^{12,14,15} and wasting and malaria severity.¹³ Most other studies have found no association between malnutrition and malaria,⁶ although several have demonstrated protective associations between worse nutritional status and malaria outcomes.^{16–19} A recent prospective study found no association between nutritional status and incident malaria, but malaria at baseline was associated with greater weight gain and reduced height gain over time.²⁰

Here, we examined the association between anthropometry and malaria infection in a population-based sample of children younger than 5 years in a region of Niger where malnutrition and malaria are co-endemic. The study population participated in a cluster-randomized trial for trachoma and all children received mass azithromycin distribution over 3 years.

MATERIALS AND METHODS

Study setting and population. The present study is a non-prespecified secondary analysis of a cluster-randomized trial in Niger, which was conducted as part of the Partnership for the Rapid Elimination of Trachoma (PRET, clinicaltrials.gov, NCT00792922).²¹ Partnership for the Rapid Elimination of Trachoma was a multicenter cluster-randomized trial conducted in the Gambia, Niger, and Tanzania. In Niger, participants were enrolled from 48 communities in six Centers de Santé Intégrées within the Matameye district in the Zinder Region. Eligibility criteria for participation in the Niger trial have been reported in depth.^{22,23} Communities with populations between 250 and 600 were eligible for participation in the trial. Communities with a trachoma prevalence of less than 10% among children younger than 72 months were excluded.

Data collection for this cross-sectional study began in May 2013, coinciding with the beginning of the lean season and

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high malaria transmission. The study area is malaria meso-endemic and affected by *Plasmodium falciparum*.²⁴ At this time, there was no seasonal malaria chemoprevention program in the study area. The only active malaria prevention program in the study area involved bed net distribution during this period.

Study design and procedures. The design and procedures of the parent trial have been previously reported.^{22,23} Briefly, communities were randomized into four arms of 12 communities each: 1) annual treatment at standard (80%) coverage, 2) annual treatment at enhanced ($\geq 90\%$) coverage, 3) biannual treatment at standard (80%) coverage, and 4) biannual treatment at enhanced ($\geq 90\%$) coverage.

In all arms, treatment was a single directly observed dose of oral azithromycin (20 mg/kg up to a maximum dose of 1 g in adults). Children younger than 6 months old, pregnant women, and those allergic to macrolides were given topical tetracycline ointment (1%). An annual population-based census was conducted to collect demographic information, monitor vital status, and assess treatment coverage over the 3-year study period. Trachoma monitoring visits were conducted biannually.

The present report includes data collected during the final study visit, 36 months after study initiation. Eligibility criteria included children aged 6–60 months residing in the 48 communities enrolled in the PRET Niger trial who were assessed for anthropometry and malaria status at the final study visit. A random sample of 62 children aged 6–60 months at the time of the final study visit per community was selected from the prior census data to include at least 50 children per community. If a community had fewer than 50 children, all children were selected. In addition to trachoma assessments, trained local study personnel collected data on anthropometric and malaria indicators from these selected children.

Anthropometry. Anthropometric assessments included height, weight, and mid-upper arm circumference (MUAC). Recumbent length was measured in children younger than 24 months and standing height was measured in children older than 24 months. Both were measured to the nearest 0.1 cm (Schorrboard; Schorr Productions LLC, Olney, MD). Children were weighed standing when possible or in the arms of a parent or guardian when necessary (Seca 874 flat digital scale; Seca GmbH & Co. KG, Hamburg, Germany). Weight was measured to the nearest 0.1 kg. Mid-upper arm circumference was assessed using a non-stretchable tape developed by Johns Hopkins University.²⁵ Mid-upper arm circumference was measured to the nearest 1 mm. All anthropometric measurements were collected in triplicate and median values were used in analyses. Study personnel referred children with severe acute malnutrition (MUAC < 115 mm) or illness to the local health posts for further evaluation and treatment.

Malaria. Malaria assessments included thick blood smears and hemoglobin concentration. Trained examiners collected thick blood smears on glass slides, which were air-dried and stored at room temperature at the Zinder Regional Hospital in Niger. The slides were stained with 3% Giemsa, and two experienced, masked microscopists used a light microscope to determine the presence of *Plasmodium* parasites. The smear was considered positive if both microscopists observed parasites and negative if the microscopists disagreed. If data were missing for one microscopist, the grade from the other microscopist was used. To evaluate parasite density, both

microscopists determined the number of asexual parasites per 200 white blood cells (assuming white blood cell count 8,000/ μ L).¹⁸ Hemoglobin concentration was assessed for all sampled children (HemoCue AB, Ångelholm, Sweden).

Variables. Outcomes included binary indicators for malaria parasitemia, clinical malaria, and parasite density. Children were classified as having malaria based on positive smears, with discordant results considered negative. Clinical malaria was defined as having a positive smear plus an objective fever of $\geq 37.5^\circ\text{C}$. Parasite density was dichotomized into high and low categories, with $\geq 5,000/\mu\text{L}$ defined as high.

Exposures included height-for-age z-score (HAZ), weight-for-age z-score (WAZ), weight-for-height z-score (WHZ), and MUAC. Z-scores were calculated with the zscore06 package in Stata version 14.2 (StataCorp, College Station, TX), which uses the 2006 World Health Organization Child Growth Standards.²⁶ Height-for-age z-score, WAZ, WHZ, and MUAC were included in models as continuous variables.

Covariates were chosen a priori and included age at the time of the study visit in months, sex, and randomization arm. Models of HAZ and WAZ did not include age as a covariate because of collinearity with HAZ and WAZ measurements.

Statistical methods. Characteristics of the study population were assessed by malaria status using proportions for categorical variables and median and inter-quartile range (IQR) for continuous variables.

We used generalized estimating equations (GEE) to examine the relationship between anthropometric indicators and malaria infection. Separate models were constructed for each comparison of outcome (malaria parasitemia, clinical malaria, and parasite density) and exposure (HAZ, WAZ, WHZ, and MUAC). All GEE models used a logit link, assumed exchangeable correlation, accounted for clustering by community, and used robust standard errors. Unadjusted models included the anthropometric indicator in question as the sole covariate. All adjusted models included sex and randomization arm as covariates. The models of WHZ and MUAC also included age.

Sensitivity analyses were performed to determine if assumptions made in the determination of the malaria outcomes affected results. Specifically, we used GEE as described previously to evaluate the association between anthropometric indicators and malaria parasitemia as determined by each microscopist separately and we evaluated parasite density as a continuous variable.

As only three variables had missing data and < 1% of data were missing for each of these variables, complete case analyses were used. All analyses were conducted using Stata version 14.2 (StataCorp).

RESULTS

In May 2013, a total of 2,604 children were selected from 48 communities in the PRET-Niger trial to participate in sample collection. Of these children, 2,071 (79.5%) were examined. For this study, 422 children were excluded (419 were more than 60 months of age at the time of examination and three had no blood samples taken). The final sample included 1,649 children aged 6–60 months with anthropometric and malaria data. The median number of children aged 6–60 months included per community was 37 (IQR 32–40). Of the 1,649 children in the final sample, 780 (47.3%) were positive for malaria parasitemia and 401 (24.3%) had clinical malaria.

Among children with malaria parasitemia, 31.9% (249/780) had parasite density $\geq 5,000/\mu\text{L}$.

Characteristics of the study population by malaria parasitemia status are shown in Table 1. Children with malaria were older than children without malaria (median 42 months versus 30 months). Median hemoglobin was lower among children with malaria (9.0 g/dL versus 9.7 g/dL). Median HAZ and WAZ were slightly higher among children with malaria than children without malaria (HAZ: -2.3 versus -2.5 ; WAZ: -1.7 versus -1.9). Weight-for-height z-score and MUAC were comparable by malaria status. Missing data included five children with no hemoglobin assessment, one outlier for HAZ that was dropped because it was related to a data entry error, one outlier for WAZ that was dropped because it was related to a data entry error, and 23 missing values for WHZ which could not be calculated.

Table 2 shows the association between anthropometric indicators and malaria outcomes in unadjusted models and models adjusted for age, sex, and randomization arm. In models examining malaria parasitemia, the adjusted odds ratio (aOR) was 1.05 (95% confidence interval [CI]: 1.00–1.10) for HAZ and 1.07 (95% CI: 0.99, 1.15) for WAZ. In models of clinical malaria, the aOR was 1.07 (95% CI: 1.02–1.11) for HAZ and 1.09 (95% CI: 1.01–1.19) for WAZ. In models of parasite density, the aOR was 1.02 (95% CI: 0.96–1.08) for HAZ and 0.98 (95% CI: 0.87–1.09) for WAZ. Sensitivity analyses did not alter results, indicating that findings did not depend on the malaria microscop or on the dichotomization of parasite density.

DISCUSSION

In this cross-sectional study, we aimed to examine the association between anthropometry and malaria among children younger than 5 years in a population-based sample in Niger. Overall, we found no association between most of the examined anthropometric indicators (HAZ, WAZ, WHZ, and MUAC) and malaria outcomes (malaria parasitemia, clinical malaria, and parasite density). There may be evidence of a risk

association between greater HAZ and clinical malaria; however, the magnitude of the effect was small (7% increase in odds of clinical malaria per 1 standard deviation increase in HAZ across all communities).

Our results are consistent with previous studies on the association between malnutrition and malaria. According to a 2015 systematic review, the majority of published studies have demonstrated no association between anthropometric parameters and malaria outcomes.⁶ Of studies examining the relationship between malnutrition and malaria incidence, 90% of statistical comparisons made found no association. Similarly, among studies examining the relationship between malnutrition and parasite density, 80% of analyses found no association. A few prospective studies have suggested an association between lower nutritional status and reduced risk of malaria.^{16–19} Among these studies, three found a protective association between stunting and malaria,^{16,18,19} and one found a protective association between wasting and subsequent malaria.¹⁷ Although the exact mechanism for this protective effect is unclear, potential mechanisms for this relationship are both behavioral (e.g., protection of malnourished children by mothers or caregivers) and biological (e.g., immunomodulation by nutritional status, or an improved ability of malnourished children to produce certain cytokines in response to stimulation by specific malarial antigens). In this population in Niger, chronically malnourished children may have had less exposure to infected mosquito bites through maternal or other physical protection, or may have had altered immune responses that would confer protection against malaria infection.

In this study, all children received oral azithromycin during mass annual or biannual distributions over 3 years. Azithromycin has some efficacy in the prevention and treatment of malaria,^{27,28} and evidence suggests that antibiotics may promote linear growth and weight gain in resource-limited settings.²⁹ A recent trial demonstrated that mass azithromycin distribution reduces all-cause child mortality,³⁰ which may occur through its effect on malaria as suggested by previous

TABLE 1

Characteristics of children aged 6–60 months at the final study visit for the Partnership for the Rapid Elimination of Trachoma-Niger trial

Characteristic	Malaria status median (IQR)* or n (%)		Total population median (IQR)* or n (%) N = 1,649†
	No malaria N = 869	Malaria N = 780	
Age (months)	30 (18–42)	42 (30–54)	30 (18–42)
Sex			
Male	415 (47.8%)	406 (52.1%)	821 (49.8%)
Female	454 (52.2%)	374 (47.9%)	828 (50.2%)
Randomization arm			
A	216 (24.9%)	197 (25.3%)	413 (25.1%)
B	186 (21.4%)	194 (24.9%)	380 (23.0%)
C	256 (29.5%)	164 (21.0%)	420 (25.5%)
D	211 (24.3%)	225 (28.9%)	436 (26.4%)
Hemoglobin (g/dL)	9.7 (8.6–10.6)	9.0 (7.8–10.1)	9.4 (8.2–10.4)
Anthropometric indicators (continuous)*			
HAZ	-2.5 (-3.5 to -1.3)	-2.3 (-3.5 to -1.0)	-2.3 (-3.5 to -1.2)
WAZ	-1.9 (-2.7 to -0.9)	-1.7 (-2.7 to -0.8)	-1.8 (-2.7 to -0.9)
WHZ	-0.7 (-1.6 to 0.0)	-0.7 (-1.5 to 0.0)	-0.7 (-1.5 to 0.0)
MUAC	14.5 (13.5–15.5)	14.5 (13.6–15.5)	14.5 (13.5–15.5)
Anthropometric indicators (binary)*			
HAZ < -2	528 (60.8%)	443 (56.8%)	971 (58.9%)
WAZ < -2	390 (44.9%)	321 (41.2%)	711 (43.1%)
WHZ < -2	139 (16.2%)	97 (12.6%)	236 (14.5%)
MUAC < 125 mm	72 (8.3%)	48 (6.2%)	120 (7.3%)

* HAZ = height-for-age z-score; IQR = inter-quartile range; MUAC = mid-upper arm circumference; WAZ = weight-for-age z-score; WHZ = weight-for-height z-score.

† Total sample includes 1,649 children aged 6–60 months for which most anthropometry and/or malaria indicators were assessed. Missing data include five children missing hemoglobin, one child missing HAZ because of a data entry error, one child missing WAZ because of a data entry error, and 23 children missing WHZ, which could not be calculated by the zscore06 program.

TABLE 2
Association between anthropometric indices and malaria outcomes

Model	Unadjusted				Adjusted*			
	OR	SE	P	95% CI	aOR	SE	P	95% CI
Malaria parasitemia†								
HAZ	1.05	0.03	0.07	1.00, 1.10	1.05	0.03	0.06	1.00, 1.10
WAZ	1.07	0.04	0.08	0.99, 1.15	1.07	0.04	0.07	0.99, 1.15
WHZ	1.04	0.04	0.36	0.96, 1.12	1.00	0.04	0.99	0.93, 1.08
MUAC	1.08	0.04	0.02	1.01, 1.16	1.00	0.04	0.97	0.93, 1.08
Clinical malaria‡								
HAZ	1.07	0.02	0.005	1.02, 1.11	1.07	0.02	0.005	1.02, 1.11
WAZ	1.09	0.05	0.03	1.01, 1.19	1.09	0.05	0.04	1.01, 1.19
WHZ	1.05	0.05	0.37	0.95, 1.15	0.99	0.05	0.90	0.90, 1.10
MUAC	1.15	0.05	0.001	1.06, 1.25	1.06	0.05	0.22	0.97, 1.16
Parasite density§								
HAZ	1.02	0.03	0.61	0.96, 1.08	1.02	0.03	0.53	0.96, 1.08
WAZ	0.97	0.05	0.65	0.87, 1.09	0.98	0.06	0.69	0.87, 1.09
WHZ	0.92	0.05	0.18	0.82, 1.04	0.89	0.05	0.06	0.79, 1.00
MUAC	1.04	0.06	0.44	0.93, 1.17	0.98	0.06	0.74	0.87, 1.10

aOR = adjusted odds ratio; CI = confidence interval; HAZ = height-for-age z-score; MUAC = mid-upper arm circumference; OR = odds ratio; SE = standard error; WAZ = weight-for-age z-score; WHZ = weight-for-height z-score.

* All models adjusted for sex and randomization arm. Models with WHZ and MUAC are also adjusted for age in months.

† Malaria parasitemia was defined as having a positive smear according to both microscopists; discordant results were considered negative.

‡ Clinical malaria was defined as having a positive smear and an objective fever of $\geq 37.5^{\circ}\text{C}$.

§ Parasite density was dichotomized into high and low categories, with $\geq 5,000/\mu\text{L}$ defined as high.

trachoma studies.^{31,32} The effect of mass azithromycin distribution on nutritional status is less clear.^{33,34} In this study population, another secondary analysis indicated that bi-annual distribution of azithromycin was associated with reduced under-5 mortality compared with annual distribution.³⁵ Overall, the distribution of oral azithromycin to this population may have affected the prevalence of both nutritional status and malaria in this setting.

Strengths of this study include the standardized data collection conducted as part of a larger randomized controlled trial and the population-based design. The population-based nature of this study allows for assessment of the relationship between anthropometry and malaria outside of a clinical setting, which may differ significantly from community-based settings. Limitations include the cross-sectional design, which inhibits our ability to assess temporality in this relationship. In addition, data collection was limited by cost and logistical constraints within the larger trial, so we were unable to adjust for all potential confounders and cannot rule out the possibility of bias. Other potential confounders include socioeconomic status (SES), in which lower SES may be associated with an increased likelihood of both malnutrition and malaria. We do not believe that omitting SES was a significant contributor to bias in this study. First, we would expect this relationship to bias the association in the opposite direction than seen in this study. With bias from confounding by SES, poor nutritional status would appear to be associated with an increased odds of malaria. Second, the included communities are relatively homogenous with little variation in SES, so we would not expect SES to be a major contributor to bias. Still, we cannot rule out the possibility that these small effect sizes were due to bias from other sources of unmeasured confounding. Given the seasonal epidemiology of malnutrition and malaria in this region of Niger, these results may not be generalizable outside of similar areas of the Sahel and sub-Saharan. However, these regions have some of the highest child mortality in the world,³⁶ and understanding the relationship between nutritional status and malaria infection is critical for designing interventions to address these conditions.

Overall, this study did not find evidence of an association between most anthropometric indicators and malaria parasitemia in a population-based sample of children younger than 5 years in Niger. Although the malaria and malnutrition seasons overlap, in this study, we did not find evidence that one condition exacerbated the other. Greater height for age may be associated with increased risk of clinical malaria, although the magnitude of the effect was small and any risk would be minimal at the population level.

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