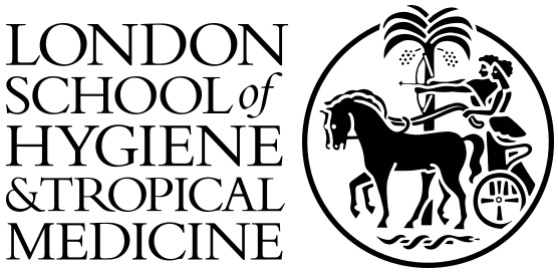

Malnutrition and malaria among children in Niger: a cross-sectional study

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ABSTRACT

The complex relationship between malnutrition and malaria affects morbidity and mortality in children under 5, 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 nutritional status and malaria infection in a population-based sample of children under 5 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 6-60 months old 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 was 1.05 (95% CI 1.00 to 1.10) for HAZ and 1.07 (95% CI 0.99, 1.15) for WAZ. In models of clinical malaria, the adjusted odds ratio was 1.07 (95% CI 1.02 to 1.11) for HAZ and 1.09 (95% CI 1.01 to 1.19) for WAZ. Overall, we did not find evidence of an association between most of the 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 globally, particularly in sub-Saharan Africa.[1] Undernutrition is directly or indirectly responsible for 45% of deaths among children under 5 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 under 5.[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 malnutrition and malaria has major impacts 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 the burden of both diseases.[6, 7] Malnutrition affects the immune system, leaving malnourished children more vulnerable to infections like 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 for malnutrition.

Previous studies on the relationship between malnutrition and malaria have found conflicting results.[6] Some studies 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] though several studies have demonstrated

protective associations between worse nutritional status and malaria outcomes.[16-19] A systematic review found significant heterogeneity in study design and methods among these studies, making it difficult to synthesize results across studies.[6]

In this cross-sectional study, we examined the association between malnutrition and malaria infection among children under 5 who were enrolled in a cluster-randomized trial for trachoma in a region of Niger where malnutrition and malaria are co-endemic.

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).[20] PRET was a multi-center cluster-randomized trial conducted in the Gambia, Niger, and Tanzania. In Niger, participants were enrolled from 48 communities in six Centres de Santé Intégrées (CSI) within the Matameye District in the Zinder Region. Eligibility criteria for participation in the Niger trial have been reported in depth.[21, 22] 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 high malaria transmission season. The study area is malaria mesoendemic and affected by *Plasmodium falciparum.*[23] 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.[21, 22] Briefly, communities were randomized into four arms of 12 communities each: 1) annual treatment at standard (80%) coverage, 2) annual treatment at enhanced (≥90%) coverage, 3) biannual treatment at standard (80%) coverage, and 4) biannual treatment at enhanced (≥ 90%) coverage.

In all arms, treatment was directly observed dose of oral azithromycin (20mg/kg up to a maximum dose of 1gm in adults). Children under 6 months of age, 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 three-year study period. Trachoma monitoring visits were conducted biannually.

The present study includes data collected during the final study visit, 36 months after study initiation. Eligibility criteria for the present study include 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 prior census data in order 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 during this study visit, 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, MD, USA). 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. MUAC was assessed using a non-stretchable tape developed by Johns Hopkins University.[24] MUAC 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 only 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 8000/µl).[18] Hemoglobin concentration was also assessed for all sampled children (HemoCue AB, Ängelholm, 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 ≥37.5˚C. Parasite density was dichotomized into high and low categories, with ≥ 5000/μL defined as high.

Exposures included height-for-age z-score (HAZ), weight-for-age z-score (WAZ), weight-for-height z-score (WHZ), and mid-upper arm circumference (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.[25] HAZ, 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 due to 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 of malnutrition and malaria. Separate models were constructed for each possible comparison of outcomes (malaria parasitemia, clinical malaria, and parasite density) and exposures (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 how assumptions made in the determination of the malaria outcomes affected results. Specifically, we used GEE as described above to evaluate the association between anthropometric indicators and malaria parasitemia as determined by each microscopist separately.

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, College Station, TX).

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 examination and 3 had no blood samples taken). The final sample included 1,649 children 6-60 months of age with anthropometric and malariometric data. The median number of children 6-60 months of age 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%) were classified as having clinical malaria. Among children with malaria parasitemia, 31.9% (249/780) had parasite density ≥ 5000/μL.

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 vs 30

months). Median hemoglobin was lower among children with malaria (9.0 g/dL vs 9.7 g/dL). Median HAZ and WAZ were slightly higher among children with malaria than children without malaria (HAZ: -2.3 vs. -2.5; WAZ: -1.7 vs -1.9). WHZ and MUAC were comparable by malaria status. Missing data included 5 children with no hemoglobin assessment, 1 outlier for HAZ that was dropped because it was related to a data entry error, 1 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 indices and malaria outcomes in unadjusted models as well as models adjusted for age, sex, and randomization arm. In models examining malaria parasitemia, the adjusted odds ratio was 1.05 (95% CI 1.00 to 1.10) for HAZ and 1.07 (95% CI 0.99, 1.15) for WAZ. In models examining clinical malaria, the adjusted odds ratio was 1.07 (95% CI 1.02 to 1.11) for HAZ and 1.09 (95% CI 1.01 to 1.19) for WAZ. In models examining parasite density, the adjusted odds ratio was 1.02 (95% CI 0.96 to 1.08) for HAZ and 0.98 (95% CI 0.87 to 1.09). Sensitivity analyses did not substantially alter results, indicating that findings did not depend on the malaria microscopist or on the dichotomization of parasite density.

DISCUSSION

In this cross-sectional study, we aimed to examine the association between malnutrition and malaria among children under 5 in a population-based sample in Niger. Overall, we found no association between most of the examined anthropometric indicators (HAZ, WAZ, WHZ, MUAC) and malaria outcomes (malaria parasitemia, clinical malaria, 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 SD 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.

Strengths of this study 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 malaria and malnutrition 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 socio-economic 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, in that bias due to SES would make poor nutritional status 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-Sahel. However, these regions have some of the highest child mortality in the world,[26] 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 indices and malaria parasitemia in a population-based sample of children under 5 in Niger. Although the malaria and malnutrition seasons overlap, in this study we did not find evidence that one condition exacerbated the other in this cross-sectional sample. Greater height for age may be associated with increased risk of clinical malaria, though the magnitude of the effect was small and any risk would be minimal at the population level.

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Disclosures

No conflicts of interest exist and none of the authors have any disclosures.

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TABLES

Table 1. Characteristics of children 6-60 months of age at the final study visit for the PRET-Niger trial

Characteristic	Malaria Status Median (IQR)[1] or n (%)		Total Population Median (IQR)[1] or n (%) n=1,649[2]
	No malaria n= 869	Malaria n=780	
Age (months)	30 (18 to 42)	42 (30 to 54)	30 (18 to 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 to 10.6)	9.0 (7.8 to 10.1)	9.4 (8.2 to 10.4)
Anthropometric indicators (continuous)[1]			
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 to 15.5)	14.5 (13.6 to 15.5)	14.5 (13.5 to 15.5)
Anthropometric indicators (binary)[1]			
HAZ <-2	528 (60.1%)	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%

[1]IQR, inter-quartile range; HAZ, height-for-age z-score; WAZ, weight-for-age z-score; WHZ, weight-for-height z-score; MUAC, mid-upper arm circumference

[2]Total sample includes 1,649 children 6-60 months of age for which most anthropometry and/or malaria indicators were assessed. Missing data include: 5 children missing hemoglobin, 1 child missing HAZ due to a data entry error, 1 child was missing WAZ due to 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[1]			
	OR	SE	*P*	95%CI	aOR	SE	*P*	95%CI
Malaria parasitemia[2]								
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[2]								
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[3]								
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

[1]All models adjusted for sex and randomization arm. Models with WHZ and MUAC are also adjusted for age in months.
[2]Malaria parasitemia was defined as having a positive smear according to both microscopists; discordant results were considered negative.
[3]Clinical malaria was defined as having a positive smear and an objective fever of ≥37.5˚C.
[4]Parasite density was dichotomized into high and low categories, with ≥ 5000/µl defined as high.