

Stunting May Determine the Severity of Malaria-Associated Anemia in African Children

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ABSTRACT. *Objective.* Evidence from previous studies that malnourished children are protected against malaria is controversial. In individuals repeatedly exposed to malaria, immunity may develop first against severe disease, then against pyrogens, and last, against parasites. If this is true, this would suggest that reduced immune function that may exist in stunted children exacerbates the severity of malarial signs and symptoms, rather than the occurrence of parasitemia. On the other hand, several studies have suggested that malnourished children are protected to some degree against malaria. Our aim was to evaluate whether observational data support the hypothesis that nutritional inadequacies that cause stunting modify the associations between malaria and hematologic indicators such as hemoglobin concentration and serum concentrations of C-reactive protein and soluble transferrin receptor (sTfR). We showed earlier that increased serum concentrations of these receptors in asymptomatic malaria may be explained, at least in part, by increased erythropoiesis to compensate for malaria-induced hemolysis.

Methodology. Community-based cluster survey among Kenyan children aged 2 to 36 months asymptomatic for malaria or anemia ($n = 318$).

Results. When adjusted for age and wasting, the malaria-associated decrease in mean hemoglobin concentration was 8.5 g/L and 15.8 g/L in nonstunted and stunted children, respectively. The malaria-associated increase in geometric mean serum concentrations of sTfR was 1.1-fold and 1.8-fold in nonstunted and stunted children, respectively. The malaria-associated increase in geometric mean serum concentrations of C-reactive protein was 1.4-fold and 2.3-fold in nonstunted and stunted children, respectively. Thus, children with malaria and those who were stunted suffered from more severe anemia and had higher serum concentrations of C-reactive protein and sTfR than would be expected from the combined effect of the 2 working independently.

Conclusions. Our results are consistent with the notion that the nutritional inadequacies causing stunting also impair host immunity, thus increasing the degree to which malaria is associated with decreased concentrations of hemoglobin, with increased inflammation, and with increased iron demand in developing erythroblasts. Increased intake of micronutrients may not only reduce stunting and nutritional anemia, but also reduce malaria-

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ABBREVIATIONS. sTfR, soluble transferrin receptor; CI, confidence interval.

Children in developing countries generally fail to achieve their genetically determined potential height because of poor diet and infection.^{1,2} It is likely that the nutritional inadequacies that cause stunting also impair host immunity, thereby increasing the incidence, severity, and duration of many infectious diseases.³

Individuals with repeated exposure to malaria are protected against severe disease and death before they develop the ability to regulate fever, parasite density, and ultimately infection in itself. This has led to the hypothesis that immunity develops first against severe disease, then against pyrogens, and lastly against parasites.⁴ If true, this would suggest that reduced immune function, such as that which may exist in stunted children, exacerbates the severity of malarial signs and symptoms, rather than the occurrence of parasitemia. On the other hand, several studies have suggested that malnourished children are protected to some degree against malaria.⁵⁻⁷

The concentration of soluble transferrin receptor (sTfR) in serum is a new indicator of iron demand by the erythroid precursor mass. It provides a measure of both the rate of erythropoiesis and the degree of iron deficiency,⁸ and is influenced little or not at all by the inflammatory response to infection. We recently reported increased serum concentrations of sTfR and C-reactive protein in children with asymptomatic malaria.⁹ These increased serum sTfR concentrations may be explained, at least in part, by increased erythropoiesis to compensate for malaria-induced hemolysis.⁹

We conducted a cross-sectional study in children aged 2 to 36 months without symptoms of malaria or anemia living in an area with seasonal malaria transmission. The aim of our study was to evaluate whether data from this survey give support to the hypothesis that the relationship between malarial parasitemia and stunting is synergistic, ie, that the presence of asymptomatic malaria and nutritional inadequacies (as indicated by stunting) results in a lower concentration of hemoglobin, and higher serum concentrations of sTfR and C-reactive protein,

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than would be expected from the combined effect of the 2 working independently.

SUBJECTS AND METHODS

Study Area

The study was conducted in the first annual rainy season (April through June) of 1997 in an area of seasonal malaria in Eastern Province, Kenya. The study area comprises ~720 km² at an altitude of 800 to 900 m above sea level, located halfway between Nairobi and Mombasa on the road and rail link. Malaria infection reported at the clinical facilities in the area are attributable exclusively to *Plasmodium falciparum*. No malaria control program is active in the area, and no epidemiologic or entomologic studies on malaria have been conducted previously.

Study Population and Sampling Procedures

The target population comprised children living in the study area aged 2 to 36 months, with no manifestations reported by mothers or caregivers that were compatible with malaria or anemia. Few of the children studied suffer from intestinal worm infections or schistosomiasis.⁹ Sampling procedures have been described in detail previously.⁹ In brief, children were selected using a 2-stage cluster sampling procedure. At the first sampling stage, 45 of 79 communities in the study area were sampled systematically, with a sampling probability proportional to size as measured by the number of households. At the second sampling stage, 12 households were randomly selected within each selected community, and all resident children with no symptoms of malaria or anemia and within the desired age range were selected for the study.

Field Procedures

Informed consent was sought and obtained from community leaders, locally active auxiliary health workers, and parents of eligible children. Children were treated as deemed necessary on completion of the survey. The study was approved by the African Medical and Research Foundation and the Kenya Medical Research Foundation, whose ethical standards were followed.

Field staff were trained in anthropometric techniques, and measurements were standardized^{10,11} before data collection. Recumbent length (<2 y) or standing height (≥2 y), body weight (Seca 720 infant scale [Hamburg, Germany], allowing for measurements to be read within 10 g), mid-upper arm circumference, and triceps skinfold thickness (Harpender calipers, CMS Weighing Equipment, London, United Kingdom) were recorded as the average of duplicate measurements, respectively.

The procedures for collection, handling, and analysis of capillary blood samples has been described elsewhere.⁹ Hemoglobin concentrations were measured using a field meter (HemoCue, Ångelholm, Sweden) and malaria was detected by microscopic examination of Giemsa-stained blood slides. Concentrations of sTfR were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). C-reactive protein concentrations were interpreted as indicators of the activity of infection and measured by a standard turbidimetric method. Intra- and inter-assay coefficients of variation for these biochemical tests are reported elsewhere.⁹

Response and Missing Values

The study included 318 children. Of 35 children who did not participate or fully participate, 14 were replaced by random selection, and weighting was used to maintain the validity of assuming an equal probability sample.^{12,13} Sample sizes reported below 318 are attributable to missing values.

Statistical Analysis

Height-for-age and weight-for-height z-scores were calculated using Epi Info v6.04 (Centers for Disease Control and Prevention, Atlanta, GA).¹⁴ Being stunted or wasted was defined by height-for-age or weight-for-height z scores < -2 standard deviations of the median of the National Center for Health Statistics reference population, respectively.¹⁵ Data were explored using SPSS (v7.5 for Windows; SPSS Inc, Chicago, IL) and analyzed using SUDAAN (stand-alone software v7.5.2a for Windows; Research Triangle Institute, Research Triangle Park NC), assuming 2-stage cluster sampling with replacement at the first sampling stage. The variance estimates under this assumption do not take into account that clusters were sampled from a finite population. Thus, the standard error values and confidence intervals reported here are overestimates, and statistical tests are conservative in detecting existing associations.

As a first analytic step, the relationships between malaria and height-for-age z score and between malaria and weight-for-height z score were assessed by logistic regression. Serum concentrations of sTfR and C-reactive protein were normalized by decimal logarithm transformations, and their relationship with stunting or wasting were assessed by linear regression analysis. Associations between height-for-age z score and age class (2–11 months, 12–23 months, >24 months) or continuous variables (weight-for-height z score, hemoglobin concentration) were assessed by analysis of variance and linear regression analysis, respectively.

Multiple linear regression was used to compare stunted and nonstunted children regarding their associations between malaria and hemoglobin concentration, or between malaria and log transformed serum concentrations of sTfR or C-reactive protein, respectively. Possible interaction was tested directly by multivariate linear regression analysis. Adjustment for age class and sex led to similar conclusions and effect estimates, so that these variables were excluded from the final model.

RESULTS

The prevalence of children who were stunted or wasted was 38.7% (95% confidence interval [CI]: 32.0–45.4) and 4.7% (95% CI: 1.6–7.8), respectively. The prevalence of malaria was 17.6% (95% CI: 11.3–23.8; *n* = 318): for age classes 2 to 11 months, 12 to 23 months, and >24 months, these figures were 12.6% (*n* = 92), 18.8% (*n* = 116), and 20.4% (*n* = 111), respectively, and for girls and boys they were 16.1% (*n* = 145) and 18.8% (*n* = 173), respectively. Other characteristics of the study population, broken down by age class and sex, are given in Table 1. Stunting was most pronounced in children aged 12 to 23

TABLE 1. Characteristics Indicating Nutritional Status of the Population Studied, by Age Class and Sex

	Height-for-Age z Score		Weight-for-Height z Score		Mid-Upper Arm Circumference, cm*		Triceps Skinfold Thickness, mm*	
Age class								
2–11 mo	-1.29 ± 1.56	(92)	-0.03 ± 0.96	(92)	14.5 [13.2–15.1]	(92)	7.51 [5.76–7.89]	(91)
12–23 mo	-2.04 ± 0.91	(113)	-0.85 ± 0.74	(113)	14.7 [13.7–15.4]	(116)	6.89 [6.00–7.85]	(114)
>24 mo	-1.93 ± 0.90	(107)	-0.88 ± 0.57	(107)	14.7 [14.1–15.4]	(108)	6.97 [6.25–7.98]	(107)
Sex								
Male	-1.90 ± 1.23	(169)	-0.59 ± 0.55	(169)	14.8 [14.0–15.4]	(146)	7.05 [5.95–7.94]	(143)
Female	-1.65 ± 0.66	(142)	-0.65 ± 0.54	(142)	14.5 [13.5–15.2]	(135)	6.93 [5.96–7.92]	(134)
All	-1.79 ± 0.81	(311)	-0.62 ± 0.42	(311)	14.6 [13.8–15.3]	(316)	6.97 [5.95–7.95]	(311)

Mean ± standard deviation or *median [interquartile range] (*n*).

Figures were derived from weighted analysis and were rounded off to integer values.

months, whose height-for-age z score was 0.75 below the value of children aged 2 to 11 months.

An increase of one unit z score of height-for-age was associated with an odds ratio of malaria of 0.87 (95% CI: 0.69–1.09; $P = .23$), a weight-for-height increase of 0.16 z scores (95% CI: 0.04–0.27; $P = .009$), and a hemoglobin concentration increase of 2.0 g/L (95% CI: 0.7–3.4 g/L; $P = .004$). Each increase of 1 unit z score of weight-for-height was associated with an odds ratio of malaria of 0.78 (95% CI: 0.58–1.05; $P = .10$) and an increase in hemoglobin concentration of 2.3 g/L (95% CI: 1.0–3.6 g/L; $P = .001$), respectively. When adjusted for wasting (weight-for-height z score quartiles), an increase of 1 unit z score of height-for-age corresponded to an odds ratio of malaria of 0.93 (95% CI: 0.73–1.17; $P = .52$). When analyzed by univariate linear regression techniques, there was no evidence of a biologically or statistically significant relationship between stunting and log transformed serum concentrations of sTfR or C-reactive protein, or between wasting and log transformed serum concentrations of sTfR or C-reactive protein (data not shown).

Univariate analysis showed that children with malaria had lower mean hemoglobin concentrations than children without malaria (92.7 g/L compared with 104.1 g/L; difference 11.3 g/L; 95% CI: 6.4–16.3 g/L; $P = .0001$). Children with malaria also had higher geometric mean serum concentrations of sTfR (11.4 mg/L compared with 7.8 mg/L; ratio 1.4; 95% CI: 1.1–1.9; $P = .005$) and C-reactive protein (12.5 mg/L compared with 6.8 mg/L; ratio 1.8; 95% CI: 1.2–2.7; $P = .004$).

Figure 1 compares stunted and nonstunted children regarding their association between malaria and hematologic indicators. There was no evidence for substantial effects of stunting on these indicators in the absence of malaria. The malaria-associated decrease in mean hemoglobin concentration was 8.6 g/L (95% CI: 2.6–14.6 g/L) in nonstunted children, and 16.4 g/L (95% CI: 9.3–23.5 g/L) in stunted children (Fig 1, top). In nonstunted children, geometric mean serum concentrations of sTfR were 1.2-fold (95% CI: 0.9–1.6) higher in children with malaria than those without malaria (Fig 1, center); in stunted children, this ratio was 1.8 (95% CI: 1.3–2.5). Among nonstunted children, geometric mean serum concentrations of C-reactive protein were 1.4-fold (95% CI: 0.8–2.3) higher in children with malaria than those without malaria (Fig 1, bottom); among stunted children, this ratio was 2.3 (95% CI: 1.2–4.7).

These relationships were further assessed by multivariate regression analysis, which was used to test the significance of product terms directly and to adjust for possible confounding by age class and wasting (entered into the model as weight-for-height z score quartiles). When so analyzed, the malaria-associated decrease in mean hemoglobin concentration was 8.5 g/L and 15.8 g/L in nonstunted and stunted children, respectively (P value of test for difference: .08). The malaria-associated increase in geometric mean serum sTfR concentrations was 1.1-fold and 1.8-fold in nonstunted and stunted children, respectively (P value of test for difference = .05). The

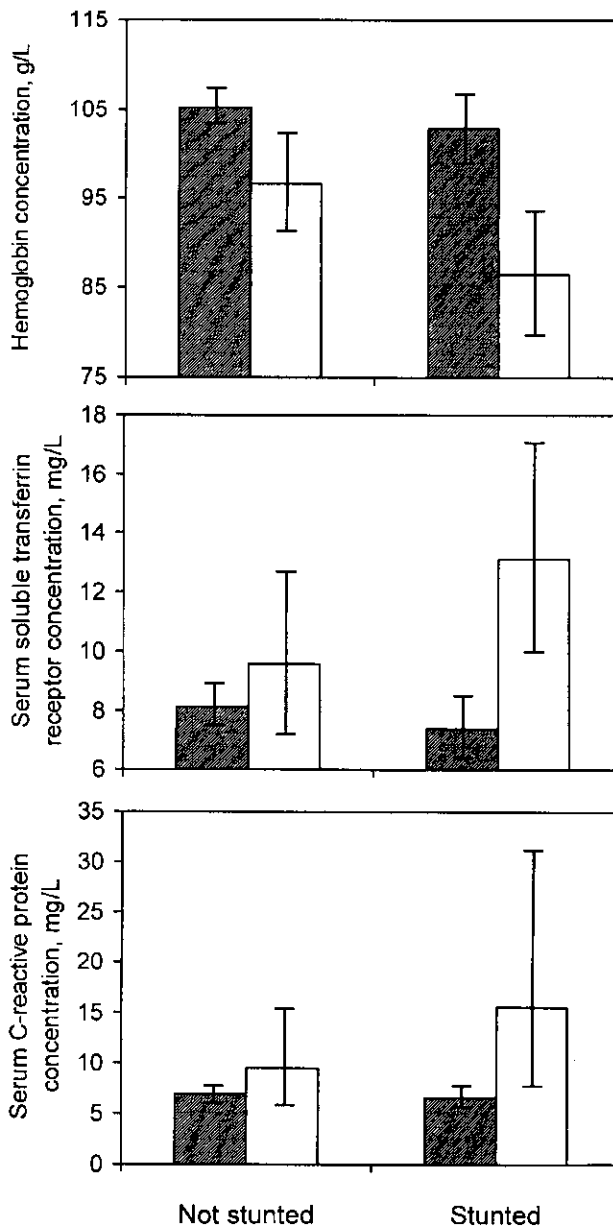


Fig 1. Modification by stunting of the relation between malaria and mean hemoglobin concentration (top; $n = 311$), and geometric mean serum concentrations of transferrin receptor (center; $n = 222$) and C-reactive protein (bottom; $n = 90$). When adjusted for age and wasting, P values indicating significance of the malaria-associated differences in these hematologic indicators were .08, .05, and .05, respectively (see text). Absence and presence of malaria are indicated by black and white columns respectively; error bars indicate 95% CIs.

malaria-associated increase in geometric mean serum concentrations of C-reactive protein was 1.4-fold and 2.3-fold in nonstunted and stunted children, respectively (P value of test for difference: .05). These effect estimates are similar for nonadjusted estimates (see previous paragraph), indicating little or no confounding by age or wasting. There was no evidence that the relationship between malaria and these hematologic indicators was modified by age (data not shown).

Missing data were mostly attributable to insuffi-

cient serum being available to determine concentrations of sTfR and serum C-reactive protein. Children with missing data ($n = 96$), and who were therefore excluded from the multiple regression analysis, did not have substantially different hemoglobin concentrations or height-for-age z scores from those who were included (not shown), although fewer of them suffered from malaria (14% compared with 25%). Selection bias would have occurred if the observed relationships were different in children with missing values.

DISCUSSION

Our findings support the hypothesis that in stunted children, malaria is associated with lower hemoglobin concentrations and higher serum concentrations of sTfR and C-reactive protein than in their nonstunted counterparts. There is no clear evidence that stunting is associated with an increased prevalence of malarial infection.

The prevalences of stunted and wasted children were 39% and 5%, respectively. The mean hemoglobin concentration was 102 g/L, and we showed earlier that the prevalence of anemia in this population was 71%.⁹ These values are typical for this age group in Kenya and other countries in Africa.¹⁶⁻¹⁹ Our study confirmed that stunting was most pronounced in children aged 12 to 23 months. This corroborates findings in most studies that stunting in developing countries peaks at the age of 24 months and stabilizes thereafter.²⁰ Missing values occurred mainly because of insufficient volume of serum being available for biochemical analysis: there is no reason to assume that this led to selection bias in the relationships observed. Our conclusions may therefore apply to African preschool children who are asymptomatic for anemia and malaria and living in areas of seasonal malaria.

Serum sTfR concentrations are closely correlated to the number of receptors expressed on the surface of erythroblasts, where they transport transferrin-bound iron into the cell. An expansion of the erythroid mass results in increased serum sTfR concentrations, and increased transferrin receptor expression takes place on the surface of iron-deficient erythroblasts. Serum sTfR concentrations thus reflect both the rate of erythropoiesis and the degree of iron deficiency in the erythron.⁸ Serum sTfR concentrations are not or only marginally influenced by the inflammatory response to infection,^{8,21} and no infections investigated so far except for malaria have been shown to be associated with serum sTfR concentrations. We proposed earlier that the observed increase in serum sTfR concentration in malaria is attributable entirely or in part to hemolysis, which occurs in malaria but is not a common feature in other infections.⁹ Malaria-induced hemolysis leads to lower hemoglobin concentrations, which in turn results in increased erythropoiesis under influence of increased production of erythropoietin. Red cell destruction may occur as a result of direct action by malaria parasites, or because a malaria-induced immune response leads to lysis of parasitized and nonparasitized red cells.²² It cannot be ruled out that, in

addition, serum sTfR concentration is increased in malaria because of ineffective erythropoiesis, whereby developing erythroblasts die prematurely in the marrow without producing mature red cells.⁹

Our findings indicate that malaria-associated anemia, iron demand, and inflammation are greater in stunted than in nonstunted children. Although it is conceivable that malaria causes stunting, we consider it more likely that nutritional inadequacies that result in stunting also exacerbate the effects of malaria, given that malarial infection is a transient condition, and stunting becomes manifest only after a prolonged period of slowing in skeletal growth. Some of these nutritional inadequacies—such as deficiencies in zinc,²³ iron^{24,25} and possibly vitamin A^{26,27}—are also known or suspected to impair host immunity.²⁸⁻³² As reviewed by Scrimshaw et al,³³ there is compelling evidence that reduced immunity due to nutritional deficiencies reduce host capacity to resist the consequences of a wide range of infections. This most likely explains the effects of malaria as observed in our study are more severe in stunted children than in their nonstunted counterparts.

Before 1950 it was widely accepted, although little supported by epidemiologic evidence, that malnutrition is associated with greater frequency and severity of malaria.³⁴ A number of influential studies subsequently appeared that in fact suggested that malnourished children are to some degree protected against malaria. However, Shankar³⁴ in a review concluded that these studies suffered from methodologic shortcomings and that the available evidence indicates that malnutrition is associated with increased occurrence of infection and symptomatic malaria, and considerably higher likelihood of malaria mortality in humans. This is in line with our findings, and implies that nutritional interventions using micronutrients may not only reduce stunting and nutritional anemia, but also reduce malaria-associated anemia. Famine or starvation may be a notable exception, because there is strong evidence that refeeding of starved individuals with latent infections carries an increased risk of symptomatic malaria. This may suggest that parasite proliferation following refeeding temporarily outpaces development of protective immunity.³⁴ We could not demonstrate an influence of wasting on malaria or malaria-associated anemia (data not shown), perhaps because few of the children studied were wasted.

CONCLUSION

Our results give observational support to the proposed hypothesis that the nutritional inadequacies that cause stunting also impair host immunity, thus increasing the degree to which malaria is associated with decreased concentrations of hemoglobin, with increased inflammation and with increased iron required for developing erythroblasts. Increased intake of micronutrients may not only reduce stunting and nutritional anemia, but also reduce malaria-associated anemia. Increased intake of micronutrients may not only reduce stunting and nutritional anemia, but also reduce malaria-associated anemia. However,

longitudinal studies are required to confirm causality.

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