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Asymptomatic *Plasmodium* Infection and Cognition among Primary Schoolchildren in a High Malaria Transmission Setting in Uganda

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Abstract. Asymptomatic parasitemia is common among schoolchildren living in areas of high malaria transmission, yet little is known about its effect on cognitive function in these settings. To investigate associations between asymptomatic parasitemia, anemia, and cognition among primary schoolchildren living in a high malaria transmission setting, we studied 740 children enrolled in a clinical trial in Tororo, Uganda. Parasitemia, measured by thick blood smears, was present in 30% of the children. Infected children had lower test scores for abstract reasoning (adjusted mean difference [AMD] −0.6, 95% confidence interval [CI] −1.01 to −0.21) and sustained attention (AMD −1.6 95% CI −2.40 to −0.81) compared with uninfected children. There was also evidence for a dose–response relationship between parasite density and scores for sustained attention. No associations were observed between anemia and either test of cognition. Schoolchildren in high transmission settings may experience cognitive benefits, from interventions aimed at reducing the prevalence of asymptomatic parasitemia.

INTRODUCTION

Parasitic disease, particularly *Plasmodium falciparum* malaria, remains a major health problem for schoolchildren in sub-Saharan Africa.[1–4] In this population, malaria is an important contributor to anemia, malnutrition, and mortality.[5,6] In addition, impaired cognition and poor school performance are important hidden burdens of malaria, which may prevent children from achieving their full educational potential.[7–12]

The health and educational burden of malaria is the result of both clinical disease and asymptomatic parasitemia, with the latter much more common than the former[13]; the consequences of asymptomatic parasitemia are likely to depend on the underlying intensity of malaria transmission. Studies conducted in settings characterized by seasonal transmission[12] or moderate transmission[10] have shown associations between asymptomatic parasitemia, poor cognitive function, and educational outcomes. Data on the impact of malaria on cognition among schoolchildren living in high transmission settings are surprisingly limited; one study conducted in western Kenya showed that three rounds of intermittent preventive treatment (IPT) significantly improved classroom attention of schoolchildren.[7] This work investigated the association between asymptomatic *Plasmodium* infection and cognitive function among schoolchildren in eastern Uganda, where malaria transmission is perennial and high, and asymptomatic *Plasmodium* infections are common.[2–4]

METHODS

Study site. The study was conducted in February 2011 in Mulanda primary school located in Mulanda sub-county, Tororo District, eastern Uganda. This area is mainly dry savannah grassland interrupted by bare rocky outcrops and lower lying swamps, although natural vegetation has mostly been replaced by cultivated crops. Tororo District is characterized by a high intensity of malaria transmission,[14] with an estimated entomological inoculation rate of 562 infective bites per person per year.[15] Transmission is bimodal, with peaks associated with the two rainy seasons. Malaria in the area is predominantly caused by *Plasmodium falciparum*[3] and *Anopheles gambiae* s.s., and to a lesser extent, *Anopheles funestus* are the main vectors.[15] In the 5 years before this study, malaria control in Tororo District was typically limited to the promotion of IPT during pregnancy, distribution of insecticide-treated nets (ITNs) through antenatal care services and malaria case management with artemisinin-based combined therapy. In January 2011, however, a mass community-based free ITN distribution campaign was conducted throughout the sub-county.

Mulanda sub-county has eight primary schools, all of which are under the government supported universal primary education scheme. Mulanda primary school was purposively selected for the study because of its large student population (1,320 students) and close proximity (approximately 500 meters) to the main public health facility in the area (Mulanda Health Center IV).

Study procedures. This study reports baseline data collected as part of a randomized placebo-controlled trial investigating the impact of IPT on malaria morbidity and cognitive function in Ugandan schoolchildren (Clinicaltrials.gov identifier NCT01231880).

All children with parental consent were screened for eligibility to join the study. Children were excluded if they had any of the following: 1) known allergy or prior adverse reaction to artemisinin-based regimens; 2) history of menarche; 3) fever (axillary temperature ≥ 37.5°C) or history of fever in previous 24 hours; 4) evidence of severe malaria or danger signs; or 5) ongoing antimalarial treatment.

At enrollment, a standardized questionnaire was administered by study personnel to children fulfilling the selection criteria to record data on socio- demographics, bed-net ownership, and bed-net use. A focused physical examination was conducted that included a general and abdominal examination as well as measurement of temperature and weight. A finger-prick blood sample was obtained for thick and thin

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blood smears to assess for *Plasmodium* infection, hemoglobin estimation, and for filter paper storage. Stool samples were also collected.

Laboratory evaluations. All blood smears were labeled and air dried at the school and subsequently stained with 2% Giemsa for 30 minutes at the health facility at the end of each day. Parasite densities were determined from thick blood smears by counting the number of asexual parasites per 200 white blood cells (or per 500 if the count was < 10 parasites/200 white cells), assuming a white blood cell count of 8,000/mL. A smear was considered negative after reviewing 100 high-powered fields. Asymptomatic malaria was defined as a positive blood smear for *Plasmodium* parasites with no associated clinical symptoms. All positive thick blood smears had corresponding thin smears viewed for species identification. Gametocytaemia was also determined from thick blood smears. Two independent microscopists read the slides, with a third microscopist resolving discrepant results. Hemoglobin concentration was assessed using a portable hemoglobinometer (HemoCue Ltd., Angelholm, Sweden) and estimated to an accuracy of 1 g/dL. Stool samples were examined microscopically for the eggs of intestinal nematodes and *Schistosoma mansoni* (the sole cause of schistosomiasis in the study area), using the Kato-Katz technique.

Cognitive function testing. Two aspects of cognition were assessed, including sustained attention assessed by a code transmission test and abstract reasoning tested using Ravens matrices. These two tests have been adapted for an African setting and used in a number of previous studies.[7,16] The test for sustained attention was adapted from the Tests of Everyday Attention for Children (TEA-Ch)[17] and was administered in groups of 15 or less in the local language, Japhadhola, which is also the language of school instruction for children in classes 1–3 in Mulanda sub-county. The test involved listening to a tape and identifying different numbers (code transmission). During the code transmission task, a list of digits was read out aloud at the speed of one per second. Children were required to listen out for a code—"the number 5 repeated twice consecutively"—and then record the two numbers that preceded the code. The test was administered at school over the weekend when there were no active classes at the school to reduce on external interference. Only children invited for the test were present at school on the testing days. Before the test, children were given three warm-up activities to familiarize them with the tape recorder, as well as assess their ability to count and write numbers. During the test of abstract reasoning, a set of geometric figures with a missing pattern was presented to the children and they were asked to identify the missing item that completes a pattern from a group of almost identical alternatives.[18]

Statistical analysis. All data were double-entered and cross-checked in a bespoke Microsoft access database (Microsoft Corp., Seattle, WA). Consistency checks were performed and all discrepancies and queries verified against original paper forms. *Plasmodium* infection was defined on the basis of expert microscopy results and the proportion of children with asymptomatic *Plasmodium* parasitemia was calculated as the number of children with any parasites (irrespective of species) on thick smear divided by the total number of children enrolled. Parasite density was categorized as above and below 1,000 parasites/μL. Anemia was defined using the World Health Organization (WHO) age-specific thresholds for hemoglobin (< 11.5 g/dL for children 6 to < 12 years of age and < 12.0 g/dL for those 12–14 years of age).[19,20] The anthropometric index z-score weight-for-age was calculated using the *egen* Stata function for standardizing anthropometric measures in children and adolescents.[21] Children were classified as underweight if they were less than two standard deviations below the reference mean. A household wealth index was created using principal component analysis of data on household possessions, utilities, and housing construction for each student.[22] Households were ranked according to their distribution along the index, which was then divided into quartiles and classified as an ordinal variable for use in multivariate analysis models. Information on maternal education was also included in the analysis, because of its key influence on children's cognition.

All statistical analyses were carried out using Stata version 12.0 software (STATA Corporation, College Station, TX). The outcomes of interest were *Plasmodium* infection and scores in the code transmission and Raven's matrices tests. Ninety-five percent binomial confidence intervals (CI) were estimated for proportions and standard deviations presented for means. Univariable associations between *Plasmodium* infection and potential risk factors were assessed using logistic regression and all variables showing an association at a 20% significance level were included into a multivariable logistic regression model. Logical model building using both forward and backward elimination was used to generate minimum adequate model using a 5% significance level; however, bed-net use, socioeconomic group, and anemia were retained as fixed terms in the model regardless of statistical significance because of their known association to *Plasmodium* infection among school-aged children.[3,23]

To investigate the association between asymptomatic *Plasmodium* infection and cognitive function, two sets of analyses, one for abstract reasoning (score 0–20) and the second for sustained attention (score 0–20) were undertaken. The effect of explanatory variables was quantified by mean differences in test performance scores using univariable and multivariable linear regression. Case re-sampling bootstrapping was used to

Table 1

Characteristics of the 740 primary schoolchildren participating in the study

Characteristic	*N* = 740
Gender (n female, %)	394 (53.2)
Mean age (SD, years)	9.8 (2.2)
Mean weight (SD, kg)	28.5 (8.2)
WAZ (z-scores < −2) (n, %)	105 (14.2)
Household (HH) owning at least one bed-net (n, %)	662 (89.5)
Bed-net use in last 24 hours (n, %)	262 (35.4)
Asymptomatic *Plasmodium* infection (n, %)	223 (30.1)
Plasmodium falciparum	204
Plasmodium malarie	11
Plasmodium ovale	4
Plasmodium vivax	4
Gametocytes present (%)	22 (3.0)
Helminths present (%)	56 (7.6)
Ascaris lumbricoides	38
Hookworms	15
Trichuris trichiura	3
Mean hemoglobin (g/dL, SD)	11.7 (1.0)
Household > 500 m from health facility (n, %)	666 (90.0)
Mean score sustained attention test (SD)	9.4 (3.4)
Mean score abstract reasoning test (SD)	8.2 (2.6)

account for non-normality of the scores. Variables identified as significant ($P < 0.2$) in univariate analysis were considered for multivariable analysis. Logical model building using both forward and backward elimination was used to generate minimum adequate models; however, helminth infection, maternal education, and anemia were retained as fixed terms in all models regardless of statistical significance because of their known effect on cognition.[24,25] Interaction was assessed on the basis of likelihood ratio test and included in the final model if $P \leq 0.05$. Sensitivity analysis explored the influence of parasite density on cognition, with densities categorized as uninfected, infected with 1–999 parasites/μL, and infected with ≥ 1000 parasites/μL.

Ethics. The study protocol was approved by the Makerere University School of Medicine Research and Ethics Committee (#2010-016) and the Uganda National Council of Science and Technology (#HS 865). Before the start of the study, investigators met with elected government representatives and community leaders to inform them of the study and explain the methodology. Written informed consent was obtained from the parents/guardians of all the children included in the study and written assent was obtained for children 8 years of age and above.

RESULTS

A total of 740 children 6 to 14 years of age were enrolled (Table 1). There were slightly more girls (53.2%) than boys, and the mean age (SD) of the children in the study was 9.8 (2.2) years. The overall prevalence of *Plasmodium* infection was 30.1% (223 of 740 (95% CI, 29.4–30.7]) with *P. falciparum* the most prevalent species at 91.5% (204 of 223). Most of parasite densities were relatively light, with 61.0% (136 of 223) infected children having parasite densities < 1000 parasites/μL. Overall, 89.5% (662 of 740) of children reported that their household owned a bed-net, but only 262 (39.6%) of these children reported sleeping under a net the previous night. The mean test score in the sustained attention test was 9.4, whereas the score in the abstract reasoning test was 8.2.

Factors associated with *Plasmodium* infection. Male sex, younger age group (6–10 years), and being underweight were significantly associated with *Plasmodium* infection (Table 2). In multivariable analysis, *Plasmodium* infection differed significantly by age group with a 71% (95% CI: 57–80%, $P < 0.001$) reduction in the odds of infection in children aged 11–14 years compared with younger children. Girls had significantly lower odds of infection than boys (odds ratio [OR] = 0.70, 95% CI: 0.50–0.98) and children who were underweight were 1.61 (95% CI: 0.71–1.41.) times more likely to have *Plasmodium* infection than children with normal weight. Interestingly, bed-net use was not significantly associated with lower odds of *Plasmodium* infection (OR = 0.99, 95% CI: 0.70–1.39).

Factors associated with poor cognition. In univariable analysis, *Plasmodium* infection, female gender, young age

TABLE 2
Univariate and multivariable analysis of factors associated with asymptomatic *Plasmodium* infection among the 740 primary schoolchildren in Tororo, Uganda*

		Univariate analysis		Multivariable analysis	
Variables	n/N with *Plasmodium* infection	Crude odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Sex					
Male	117/346				
Female	106/394	0.72 (0.53–0.99)	0.032	0.70 (0.50–0.98)	0.040
Age group (years)					
6–10	175/448				
11–14	48/292	0.31 (0.21–0.44)	< 0.001	0.29 (0.20–0.43)	< 0.001
WAZ (z-scores)					
Not wasted	182/635				
Wasted	41/105	1.59 (1.04–2.45)	0.033	1.61 (1.02–2.53)	0.040
Bed-net use in last 24 hours					
No	139/478				
Yes	84/262	1.15 (0.83–1.59)	0.398	0.99 (0.71–1.41)	0.987
Helminth infection					
None	204/684				
Ascaris lumbricoides	11/38	0.95 (0.47–1.96)	0.908		
Hookworms	6/15	1.56 (0.55–4.46)	0.399		
Trichuris trichiura	2/3	4.70 (0.42–52.1)	0.207		
Anemia					
No	132/420				
Yes	91/320	0.86 (0.63–1.19)	0.380	0.89 (0.64–1.25)	0.498
Distance to HF					
≤ 500 m	21/74				
> 500 m	202/666	1.09 (0.64–1.87)	0.729		
Socioeconomic group					
Poorest	63/196				
Poor	66/241	0.79 (0.52–1.20)	0.279	0.85 (0.55–1.31)	0.457
Less poor	32/120	0.77 (0.46–1.27)	0.303	0.80 (0.48–1.36)	0.418
Least poor	62/183	1.08 (0.70–1.66)	0.719	1.23 (0.79–1.94)	0.347
Maternal education					
None	21/71				
Primary	187/622	1.02 (0.59–1.75)	0.932		
Above primary	15/47	1.12 (0.50–2.48)	0.787		

*CI = confidence interval; WAZ = weight for age z-score; HF = health facility.

TABLE 3
Factors associated with poor performance in the abstract reasoning (Raven's test) among the 740 primary schoolchildren in Tororo, Uganda

Variables	n	Mean score 1–20 (SD)	Un-adjusted Mean difference between test performance	*P* value	Adjusted mean difference between test performance	*P* value
Plasmodium infection status						
Not infected	517	8.5 (2.8)				
Infected	223	7.5 (2.0)	−1.0 (−1.33, −0.67)	< 0.001	−0.6 (−1.01, −0.21)	0.001
Sex						
Male	346	8.5 (3.1)				
Female	394	7.9 (2.2)	−0.6 (−0.94, −0.21)	0.002	−0.2 (−0.61, 0.15)	0.234
Age group (years)						
6–10	448	7.4 (2.1)				
11–14	292	9.4 (2.9)	1.9 (1.59, 2.39)	< 0.001	2.4 (1.68, 3.10)	< 0.001
WAZ (z-scores)						
Not wasted	635	8.23 (2.7)				
Wasted	105	8.26 (2.4)	0.03 (−0.45, 0.51)	0.897	0.2 (−0.30, 0.61)	0.613
Bed-net use in last 24 hours						
No	478	8.3 (2.5)				
Yes	262	8.1 (2.8)	−0.2 (−0.65, 0.23)	0.347		
Helminth infection						
None	684	8.3 (2.7)				
Ascaris lumbricoides	38	7.4 (2.1)	−0.9 (−1.66, −0.11)	0.025	−1.4 (−2.11, −0.74)	< 0.001
Hookworm	15	7.1 (2.0)	−1.2 (−2.18, −0.17)	0.022	−0.1 (−0.82, 0.64)	0.810
Trichuris trichiura	3	8.0 (2.6)	−0.3 (−2.82, 2.19)	0.809	1.6 (−3.04, 6.16)	0.506
Anemia						
No	420	8.3 (2.8)				
Yes	320	8.1 (2.5)	−0.2 (−0.61, 0.13)	0.203	−0.01 (−0.44, 0.41)	0.954
Distance to HF						
≤ 500 m	74	8.5 (2.6)				
> 500 m	666	8.2 (2.6)	−0.3 (−0.93, 0.29)	0.304		
Socioeconomic group						
Poorest	196	7.7 (2.3)				
Poor	241	8.1 (2.5)	0.4 (−0.02, 0.87)	0.059	0.3 (−0.12, 0.69)	0.162
Less poor	120	8.4 (2.8)	0.7 (0.13, 1.31)	0.017	0.7 (0.17, 1.25)	0.010
Least poor	183	8.8 (3.1)	1.1 (0.60, 1.65)	< 0.001	1.03 (0.51, 1.54)	< 0.001
Maternal education						
None	71	8.3 (2.7)				
Primary	622	8.2 (2.6)	−0.1 (−0.73, 0.44)	0.623	−0.2 (−0.83, 0.26)	0.301
Above primary	47	8.7 (3.3)	0.4 (−0.70, 1.47)	0.487	−0.1 (−1.14, 0.99)	0.892

Univariate and multivariable mean differences in test scores with 95% confidence intervals (CI).
Age confounded *Plasmodium* infection and helminth infection. Socioeconomic group confounded of weight for age z-score (WAZ) scores, helminth infection status and maternal education.
Interaction between age and sex, as well as sex and helminth infection.

(6–11 years), socioeconomic group, and infection with either *Ascaris lumbricoides* or hookworm were associated with low scores in the abstract reasoning (Table 3). In multivariable analysis, children with *Plasmodium* infection scored significantly lower in the abstract reasoning test than uninfected children (mean difference −0.6 95% CI: −1.01 to −0.21). Sensitivity analysis of the influence of parasite density suggested that mean differences did not increase with increasing parasite density: 8.5 (SD = 2.8) among uninfected children; 7.5 (2.0) among children with 1–999 parasites/μL; and 7.4 (2.1) among children with ≥ 1,000 parasites/μL. The multivariable analysis also showed that children infected with *A. lumbricoides* had lower scores than children uninfected, younger children (6–10 years) performed worse than older children (11–14 years), and scores improved with increasing socioeconomic status. Although hookworm infection and female gender were associated with lower scores in the abstract reasoning test in univariate analysis, these associations were not significant after adjusting for potential confounders.

Results for the analysis of associations between sustained attention and several child level variables are presented in Table 4. In both univariable and multivariable analyses, *Plasmodium* infection was significantly associated with lower scores in the sustained attention test (adjusted mean difference: −1.6 CI −2.49 to −0.81). Sensitivity analysis indicated that mean scores decreased with increasing parasite density: 9.8 (SD = 3.5) among uninfected children; 8.7 (3.1) among children with 1–999 parasites/μL; and 7.7 (2.3) among children with ≥ 1,000 parasites/μL. The adjusted mean difference was −1.4 (−2.24, −0.60) and −1.9 (−1.23, −0.90), respectively. In addition, younger age (6–10 years) was significantly associated with lower mean scores compared with the older age (11–14years) in this test. Although girls had lower scores than boys in univariate analysis, this association was not significant after multivariable analysis. Scores in the sustained attention test was only marginally associated with socioeconomic status. Infection with helminths, anemia, and maternal education were found not to be associated with scores in the sustained attention test.

DISCUSSION

Targeting interventions to improve the educational performance of schoolchildren requires an understanding of factors affecting health and cognition, such as malaria. There is limited evidence on the impact of asymptomatic *Plasmodium* infection on cognition among school children and to our knowledge our study is one of the few that have investigated this relationship in a high malaria transmission setting in Africa. Results from this study show that asymptomatic

Table 4
Factors associated with poor performance in the sustained attention (code transmission test) among the 740 primary schoolchildren in Tororo, Uganda*

Variables	n	Mean score 1–20 (SD)	Unadjusted mean difference between test performance	*P* value	Adjusted mean difference between test performance	*P* value
Plasmodium infection						
Not infected	517	9.8 (3.5)				
Infected	223	8.3 (2.8)	−1.5 (−2.01, −0.99)	< 0.001	−1.6 (−2.40, −0.81)	< 0.001
Sex						
Male	346	9.6 (3.6)				
Female	394	9.1 (3.1)	−0.5 (−1.04, −0.03)	0.038	−0.5 (−1.20, 0.13)	0.115
Age group (years)						
6–10	448	8.4 (2.8)				
11–14	292	10.8 (3.6)	2.4 (1.88, 2.83)	< 0.001	1.6 (0.94, 2.22)	< 0.001
WAZ (z-scores)						
Not wasted	635	9.4 (3.4)				
Wasted	105	9.0 (3.2)	−0.4 (−1.11, 0.21)	0.186	−0.2 (−0.76, 0.34)	0.461
Bed-net use in last 24 hours						
No	478	9.5 (3.5)				
Yes	262	9.1 (3.1)	−0.4 (−0.92, 0.06)	0.089		
Helminth infection						
None	684	9.4 (3.4)				
Ascaris lumbricoides	38	8.8 (2.4)	−0.6 (−1.29, 0.07)	0.080	−0.2 (−0.87, 0.48)	0.573
Hookworms	15	7.8 (3.2)	−1.6 (−3.18, −0.04)	0.044	−0.7 (−2.51, 1.08)	0.437
Trichuris trichiura	3	9.6 (2.3)	0.2 (−2.14, 2.53)	0.873	1.9 (−0.03, 3.81)	0.047
Anemia						
No	420	9.5 (3.4)				
Yes	320	9.2 (3.3)	−0.30 (−0.67, 0.15)	0.191	−0.1 (−0.54, 0.36)	0.709
Distance to HF						
≤ 500 m	74	9.48 (3.2)				
> 500 m	666	9.40 (3.4)	−0.1 (−0.95, 0.79)	0.855		
Socioeconomic group						
Poorest	196	8.9 (3.4)				
Poor	241	9.4 (3.2)	0.4 (−0.16, 0.97)	0.163	0.2 (−0.37, 0.75)	0.513
Less poor	120	9.8 (3.7)	0.8 (−0.01, 1.52)	0.053	0.7 (−0.01, 1.49)	0.051
Least poor	183	9.7 (3.5)	0.7 (−0.09, 1.43)	0.086	0.6 (−0.82, 1.19)	0.088
Maternal education						
None	71	9.8 (3.8)				
Primary	622	9.4 (3.3)	−0.4 (−1.33, 0.52)	0.386	−0.4 (−1.14, 0.39)	0.346
Above primary	47	9.7 (3.3)	−0.04 (−1.39, 1.32)	0.957	−0.3 (−1.38, 0.75)	0.560

*Univariable and multivariable mean differences in test scores with 95% confidence intervals (CI).
Age confounded *Plasmodium* infection and Helminth infections. Socioeconomic group confounded maternal education.
Interaction between sex and *Plasmodium* infection and sex with age.

Plasmodium infections are strongly associated with poor performance in tests of abstract reasoning and sustained attention. Interestingly, the adjusted mean difference is greater for sustained attention than abstract reasoning. Additionally, there was evidence of a dose–response relationship between parasite density and sustained attention, but not between parasite density and abstract reasoning. By contrast, the association of scores with socioeconomic status was greater for abstract reasoning than for sustained attention.

The observed association of asymptomatic *Plasmodium* infection and cognitive scores may be a consequence of repetitive infections having direct effect on cognition[8,26,27]; another mechanism that has been suggested in the literature that could explain cognitive impairment is through the effect of iron deficiency anemia[28–31] after repeated episodes of asymptomatic infections. However, in our study, anemia was not associated with poor cognition, suggesting that the effects of the infection may be more direct, possibly involving an immunological pathway.[32]

Our results corroborate those from studies in Yemen[10] and Mali,[12] where parasitemic school-aged children performed worse than non-infected children in the tests of cognitive function, including attention, and from studies that report a cognitive improvement following malaria control.[7,33] The findings also support studies, which showed that severe and/or cerebral malaria is associated with cognitive impairment.[34–37] For example, John and others[35]found that cerebral malaria is associated with cognitive impairment at 2 years follow-up. Interestingly, Bangirana and others[37] in a subsequent study noted that malaria neurological involvement results in behavior problems at 3 months follow-up, but only affected sustained attention minimally, suggesting cognitive impacts of malaria may be gradual with less effect in the short term compared with the long term. Such a suggestion may help interpret the observed dose–response relationship between parasite density and sustained attention scores, whereby denser (and hence assumed more chronic) infection were associated with lower scores.

It is additionally noteworthy that in our study there was evidence of an association between socioeconomic status and scores of abstract reasoning, however there was little evidence of an association between socioeconomic status and scores of sustained attention. Previous authors including John and others[35] have suggested that attention measures tend to be more sensitive to proximal brain/behavior effects from malaria, whereas executive functions, such as abstract reasoning, are more affected by distal effects of poverty.

Our findings differ from recent findings from coastal Kenya[16] where there was no observed association between *P. falciparum* and performance in the same tests of cognitive function as used in this study. It is possible that these differing results are a consequence of differences in underlying intensity of malaria: moderate transmission in coastal Kenya versus high transmission in Uganda. Another possible reason for the differing results is a stronger influence of poverty on cognitive outcomes in coastal Kenya, where poverty and educational indicators are the lowest in Kenya.[38] In such a setting, any effect of *Plasmodium* infection on cognitive is overshadowed by distal effects of poverty.

The results also show potentially important variation in cognitive scores between age groups and by helminth infection status. The observed association between low scores in the abstract reasoning test and *A. lumbricoides* infection corroborates previous findings where infection was strongly related to cognitive function in schoolchildren.[39–42] The effect on cognition could be explained by the parasites leading to under-nutrition and therefore poorer growth rates of the infected children.[41,43,44] The lack of observed association between helminth infections and sustained attention may not necessarily reflect an absence of effect but may be caused by the cross-sectional design of the study, such that we were unable to capture the effects of chronic infection over an extended period.[41]

Our findings must be viewed in light of limitations inherent to a cross-sectional study design and issues related to determining causality. However, we believe that reverse causality is unlikely to explain our findings because cognitive ability is unlikely to lead to *Plasmodium* infection. A further problem with interpretation of these findings arises from the potential for confounding, as any association found in this study may have resulted from a codependence of cognitive function on a third variable. Our study was designed to minimize this problem by sampling a wide range of potential confounders including age, gender, helminth infection, anemia, maternal education, and socioeconomic status, which we controlled for in the final analysis.

In conclusion, our study results provide evidence of a strong association between asymptomatic *Plasmodium* infection and poor cognition among primary schoolchildren in a high transmission setting, with a greater apparent effect on sustained attention than on abstract reasoning. Future analyses of the main trial will report the impact of averting malaria on the health and cognition of these children.

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