The causal effect of malaria on stunting: a Mendelian randomization and matching approach

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Accepted 21 May 2013

Background

Previous studies on the association of malaria and stunted growth delivered inconsistent results. These conflicting results may be due to different levels of confounding and to considerable difficulties in elucidating a causal relationship. Randomized experiments are impractical and previous observational studies have not fully controlled for potential confounding including nutritional deficiencies, breastfeeding habits, other infectious diseases and socioeconomic status.

Methods

This study aims to estimate the causal effect between malaria episodes and stunted growth by applying a combination of Mendelian randomization, using the sickle cell trait, and matching. We demonstrate the method on a cohort of children in the Ashanti Region, Ghana.

Results

We found that the risk of stunting increases by 0.32 (P-value: 0.004, 95% CI: 0.09, 1.0) for every malaria episode. The risk estimate based on Mendelian randomization substantially differs from the multiple regression estimate of 0.02 (P-value: 0.02, 95% CI: 0.003, 0.03). In addition, based on the sensitivity analysis, our results were reasonably insensitive to unmeasured confounders.

Conclusions

The method applied in this study indicates a causal relationship between malaria and stunting in young children in an area of high endemicity and demonstrates the usefulness of the sickle cell trait as an instrument for the analysis of conditions that might be causally related to malaria.

Keywords

Malaria, stunting, children, Mendelian randomization, matching

Introduction

It is estimated that there were 174 million cases of malaria and 596,000 malaria-related deaths in sub-Saharan Africa in 2010.1 In addition to being one of the major causes of death in early childhood, repeated malaria episodes are a major cause of chronic anaemia and may impair child growth and development.2 Consequently, it is important to study the impact of malaria on child development to prioritize public health resources.

Previous epidemiological studies on the association between malaria and child growth have produced
inconsistent results; this is partly rooted in different methodological approaches. Several studies assessed growth using the mean height-for-age Z-score, whereas other studies used the prevalence of stunting (height-for-age Z-score < −2) as an indicator of insufficient growth. Stunting is a common condition in African children and is often used to assess chronic malnutrition, which is one of the main determinants of childhood morbidity and mortality. In 1956 a study from Gambia first showed a tendency to higher mean Z-scores in infants who received malaria prophylaxis compared with children who did not. Later an association between malaria and growth or risk of stunting was also seen in Nigeria, Kenya, Gambia, Ghana and Uganda. Other studies, however, found no association or even a higher risk of malaria in children with better Z-scores. Finally, one study demonstrated that the association between stunting and malaria might be strongest in young children.

A major limitation common to all previous studies is the inability to fully adjust for confounding. Specifically, nutritional deficiencies are important potential confounders because they are an important determinant of stunting and also compromise immune function, which could result in a higher risk of infection. Further potential confounders are socioeconomic status, living conditions and other infections. In addition, reverse causality in the association of stunting and malaria seems possible. Randomized trials recruiting children at birth could account for potential confounders and reverse causality but are impractical in this context.

In this paper, we seek to control for confounders in estimating the causal effect of malaria on stunting by using a combination of Mendelian randomization (MR) and matching. The basic idea of MR is to extract variation in an exposure (i.e. malaria) that is due to a gene, which is independent of confounders, and use this confounder-free variation to estimate the effect of the exposure on the outcome (i.e. stunting). The haemoglobin variant HbS, which is caused by a point-mutation at the sixth position of the β-Globin gene (β6Glu → Val), serves as the paradigm for balanced polymorphisms; whereas people homozygous for HbS (HbSS) have sickle cell disease with an increased mortality, heterozygote carriers (HbAS, sickle cell trait) are asymptomatic and protected from malaria. A previous analysis of the current data showed a negative association between the HbAS genotype and stunting in an area of high malaria endemicity and computed the magnitude of the association. However, the study did not analyse the effect of malaria on stunting or the magnitude of such an effect. In this analysis we use HbAS as a Mendelian gene to expand on this finding and estimate the effect of malaria on stunting. To control for measured confounders (e.g. birthweight, ethnic group, mosquito protection) we will use matching.

### Methods

#### Study population and design

The study was conducted in the Ashanti region in Ghana. A cohort of 1070 infants was recruited as part of a clinical trial on intermittent preventive treatment with sulphadoxine-pyrimethamine (SP). Infants were recruited at 3 months of age and followed up monthly until age 2 years with comprehensive examinations including a standardized medical history, a measurement of body temperature and a thick-and-thin smear for microscopic malaria diagnostics. Passive case detection was performed between scheduled visits. A child was diagnosed with malaria if he or she had a parasite density of more than 500 parasites/µl and a body temperature greater than 38°C or the mother reported a fever within the last 48 h. In 3-monthly intervals, standardized anthropometric measurements, including height and weight, were performed. A child was deemed stunted if his or her length/height-for-age Z-score was less than −2 (i.e. moderate or severe stunting). Further details of the study population are published in a previous paper.

#### Definition of instrument, exposure and outcome

For this analysis only infants with heterozygote HbAS or wildtype HbAA were considered. Children with homozygote mutation (HbSS) or a different mutation on the same gene leading to haemoglobin C (HbAC, HbCC, HbSC) were excluded. The instrument was a binary variable indicating the HbAS or HbAA genotype. The exposure of interest was the malarial history defined as the total number of malaria episodes during the study. The outcome of interest was whether the child was stunted at the last recorded visit, which took place when the child was approximately 2 years old.

#### Assumptions for Mendelian randomization

A combination of prior biological and clinical evidence along with empirical methods was used to assess the sickle cell trait as a valid instrument for MR. In particular, the sickle cell trait must satisfy the following assumptions (Figure 1) to be a valid instrument and to provide an unbiased estimate of the causal effect between malaria and stunting: (1) the sickle cell trait is associated with malaria episodes; (2) there are no unmeasured confounders that are associated with the sickle cell trait and stunted growth; and (3) all directed pathways from the sickle cell trait to stunting pass through malaria episodes (i.e. there is no pathway that goes directly from the sickle cell genotype to stunted growth).

Assumption (1) states that the sickle cell trait must be associated with malaria episodes. A strong association is preferred between these two variables because it leads to lower-variance estimates of the causal
A review of previous literature found numerous associations between two variables indicates no relationship between them. Numbers (1, 2, 3) represent MR assumptions and dashed arrows indicate possible violations of these assumptions as outlined in the methods section.

Matching
To control for potential confounders of the sickle cell trait-stunting relationship, one child with HbAS was matched with five children with HbAA, based on characteristics that were previously found to be associated with malaria risk and could therefore act as potential confounders (Table 1). Specifically, we matched for all measured covariates, which are birthweight, sex, birth season, ethnic group, presence of alpha-thalassaemia, village of birth, mother’s occupation, mother’s education, family’s financial status, mosquito protection and treatment arm of the original trial (SP vs placebo). We used propensity score caliper matching with rank-based Mahalanobis distance to measure covariate similarity between children. Propensity scores were calculated by logistic regression. The propensity score here was on an instrumental propensity score, which is the probability of having the sickle cell trait given the measured confounders (J. Cheng. Using the instrumental propensity score in observational studies for causal effects. Unpublished presentation. Joint Statistical Meeting, American Statistical Association, 3 August 2011). Children with missing values in the covariates were matched to other children with similar patterns of missing data. Once the measurement of covariate similarity was calculated, the matching algorithm matched each child with HbAS to five children with HbAA in such a way that their covariates are similar.

Estimation of effect ratio
We estimated the effect ratio, which measures the effect of a change in malaria episodes on the risk of stunting. For example, if the sickle cell trait were to reduce malaria episodes by 0.5 per child and this resulted in a reduction of stunting by 0.05, the effect ratio would be 0.05/0.5 = 0.1. Under the assumption that the effect of changing the rate of malaria episodes per child by A is proportional to the effect of HbAS that reduces malaria episodes by B, i.e. the effect of changing the rate of malaria episodes per child by A is C(A/B), where C is the effect of the sickle cell trait on stunting, we can interpret such an effect ratio of 0.1 as meaning that for every 10 malarial infections, one of them would lead to stunted growth. For a discussion of when such a proportionality assumption is justified, refer to these studies.

The effect ratio was estimated with a modified sign-score statistic. The distribution of this statistic is approximated by its asymptotic distribution (see...
We used this asymptotic distribution to obtain inference about the effect ratio, compute its power under the current sample size and derive confidence intervals. For details on the power calculation see Supplementary Data Section 1.5 (available as Supplementary data at *IJE* online). For comparison, we computed the multiple regression estimate of the effect ratio, an estimate that only adjusts for measured confounding, not for unmeasured confounding. This estimate is derived from a multiple linear regression with stunting as the dependent variable and all measured confounders and the number of malaria episodes as independent variables. From the regression, we take the estimated slope coefficient for malaria episodes, which is the reduction in the risk of stunting per malaria episode.

### Sensitivity analysis

To quantify the effect of unmeasured confounders on the obtained inference, a sensitivity analysis was performed. We used a standard sensitivity analysis for multiple controls with a sign-score statistic and its interpretation in higher dimensions. Specifically, we consider a binary unmeasured confounder that

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**Table 1** Characteristics of study participants at recruitment

<table>
<thead>
<tr>
<th></th>
<th>HbAS (n = 110)</th>
<th>HbAA before matching (n = 774)</th>
<th>HbAA after matching (n = 550)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birthweight, mean (SD)</td>
<td>3112.44(381.9)</td>
<td>2978.7(467.9)****</td>
<td>3065.2(390.1)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>46.4% Male</td>
<td>51.0% Male</td>
<td>51.1% Male</td>
</tr>
<tr>
<td>Birth season (dry/rainy)</td>
<td>56.4% Dry</td>
<td>55.3% Dry</td>
<td>55.6% Dry</td>
</tr>
<tr>
<td>Ethnic group (Akan/Northerner)</td>
<td>86.4% Akan</td>
<td>88.8% Akan</td>
<td>90.9% Akan</td>
</tr>
<tr>
<td>α-globin genotype (norm/hetero/homo)</td>
<td>75.7%/21.5%/2.8%</td>
<td>74.4%/23.1%/2.6%</td>
<td>76.7%/20.9%/2.4%</td>
</tr>
<tr>
<td><strong>Village composition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Village of birth:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afamanso</td>
<td>4.5%</td>
<td>4.8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Agona</td>
<td>10.0%</td>
<td>13.6%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Asamang</td>
<td>13.6%</td>
<td>11.1%</td>
<td>12.72%</td>
</tr>
<tr>
<td>Bedomase</td>
<td>5.5%</td>
<td>4.5%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Bipoa</td>
<td>14.5%</td>
<td>10.7%</td>
<td>13.3%</td>
</tr>
<tr>
<td>Jamasi</td>
<td>15.5%</td>
<td>13.8%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Kona</td>
<td>16.4%</td>
<td>12.8%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Tano-Odumasi</td>
<td>4.5%</td>
<td>12.3%**</td>
<td>5.6%</td>
</tr>
<tr>
<td>Wiamoase</td>
<td>15.5%</td>
<td>16.4%</td>
<td>18.0%</td>
</tr>
<tr>
<td><strong>Mother and household</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s occupation (non-farmer/farmer)</td>
<td>79.0% Non-farmer</td>
<td>77.7% Non-farmer</td>
<td>81.1% Non-farmer</td>
</tr>
<tr>
<td>Mother’s education (literate/illiterate)</td>
<td>91.7% Literate</td>
<td>90.5% Literate</td>
<td>95.1% Literate</td>
</tr>
<tr>
<td>Family’s financial status (good/poor)</td>
<td>69.1% Good</td>
<td>70.1% Good</td>
<td>70.9% Good</td>
</tr>
<tr>
<td>Mosquito protection (none/net/screen)</td>
<td>55.7%/32.0%/12.4%</td>
<td>45.4%*/35.1%/19.5%</td>
<td>50.8%/35.2%/14.0%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(sulphadoxine-pyrimethamine/Placebo)</td>
<td>49.1% Placebo</td>
<td>50.1% Placebo</td>
<td>48.4% Placebo</td>
</tr>
</tbody>
</table>

We conducted hypothesis tests to examine the differences between children with HbAS and HbAA for each covariate. *P*-values were obtained by doing a Pearson’s chi-square test for categorical covariates and two-sample *t*-tests for numerical covariates. For the covariate α-globin genotype, norm indicates wildtype, hetero indicates α-thalassaemia, and homo indicates homozygote α+-thalassaëma.

***P < 0.01; **P < 0.05; *P < 0.1. Before matching, some characteristics between HbAS and HbAA show *P*-values < 0.10. After matching, all the characteristics between HbAS and HbAA are not statistically different from each other.

**Supplementary data** Section 1.3, available as Supplementary data at *IJE* online. We used this asymptotic distribution to obtain inference about the effect ratio, compute its power under the current sample size and derive confidence intervals. For details on the power calculation see Supplementary Data Section 1.5 (available as Supplementary data at *IJE* online). For comparison, we computed the multiple regression estimate of the effect ratio, an estimate that only adjusts for measured confounding, not for unmeasured confounding. This estimate is derived from a multiple linear regression with stunting as the dependent variable and all measured confounders and the number of malaria episodes as independent variables. From the regression, we take the estimated slope coefficient for malaria episodes, which is the reduction in the risk of stunting per malaria episode.
has a specified effect on the odds of inheriting HbAS over HbAA and specified effect on the odds of stunting (conditional on measured confounders), and evaluate the effect such an unmeasured confounder would have on the inference we make (see Supplementary data Section 1.4, available as Supplementary data at IJE online).

Results

Basic data

The analysis was conducted on 884 children with HbAA or HbAS genotype: 774 children were HbAA homozygotes; 110 children were HbAS heterozygotes; 35 children (4.0%) were already stunted at the beginning of the trial and, by the end, 168 children (19.0%) were stunted. The t-statistic to test the difference in the time of the last recorded visit among HbAA and HbAS children did not indicate any variation \( P = 0.21, 95\% \text{ CI: } (-3.70, 16.68) \).

Table 1 shows characteristics of the HbAS and HbAA subjects. The first two columns of numbers compare the HbAS and HbAA groups before matching. Before matching, most characteristics at recruitment were similarly distributed between children with HbAS and HbAA. The notable exception is birthweight. There was evidence that birthweight of children with HbAA was lower than that of children with HbAS \( P = 0.006, 95\% \text{ CI: } (-228.27, -39.14) \).

We characterize the effect of the sickle cell trait on malaria as based on a Poisson regression. As expected, the sickle cell trait was protective against malaria. The HbAS group had fewer malaria episodes than the HbAA group before matching \( \text{RR} = 0.82, P = 0.02, 95\% \text{ CI: } 0.70, 0.97 \) and after matching \( \text{RR} = 0.82, P = 0.03, 95\% \text{ CI: } 0.70, 0.97 \). This is in alignment with previous literature on the relationship between sickle cell genotype and malaria for these data.24

Matching

The first and third columns of numbers in Table 1 compare the HbAS and HbAA groups after matching. After matching, all confounders between children with HbAA and HbAS were similarly distributed. Specifically, after running a simple hypothesis test for each covariate, with the null of no difference between HbAA and HbAS, all the \( P \)-values were well above 0.10.

Effect ratio

Using a multiple regression analysis that does not control for unmeasured confounders, the effect ratio was estimated at 0.02 \( P = 0.02, 95\% \text{ CI: } 0.003, 0.03 \), indicating only a weak association between malaria and stunting (Table 2).

When the sickle cell trait is used to control for unmeasured confounding, the effect ratio was estimated at 0.32 \( P = 0.004, 95\% \text{ CI: } 0.09, 1 \). That is, for every unit increase in malaria episodes, there is an average 0.32 increase in the risk of stunting.

Sensitivity analysis

Our analysis indicated that malaria causes stunting under the assumptions described in the methods section. The results of the sensitivity analysis, which we performed to assess the sensitivity of our results against a violation of Assumption (2) that HbAS must be independent of unmeasured confounders, is presented in Figure 2.

The plot shows the potential effect of a binary unmeasured confounder on the odds of stunting \( x \)-axis) and the odds of inheriting HbAS \( y \)-axis). Any points between the curves represent an unmeasured confounder whose effect on stunting \( x \)-axis) and the sickle cell trait \( y \)-axis) does not change the inference that malaria causes stunting. The bold curves represent the boundaries for which the inference that malaria causes stunting would no longer hold due to unmeasured confounders. For example, the point \((2.0, 1.75)\) represents an unmeasured confounder that increases the odds of stunting by a factor of 2 and increases the odds of inheriting HbAS over HbAA by a factor of 1.75; this point is between the two bold curves and its associated \( P \)-value is between 0.025 and 0.05, indicating strong evidence that malaria causes stunting even if such an unmeasured confounder existed. On the other hand, an unmeasured confounder associated with increasing the odds of stunting by a factor of at least 1.75 and increasing the odds of inheriting HbAS over HbAA by a factor of at least 2.5 lies outside the bolded curves, indicating at most weak evidence for an effect of malaria on stunting.

Discussion

By using MR with the sickle cell trait as the instrument and matching techniques to account for potential confounders, we found evidence of a causal effect of malarial episodes on stunting. Each increase by one malaria episode increased the risk of stunting by 0.32 \( 95\% \text{ CI: } 0.09, 1 \), indicating that the effect of malaria on stunting is substantial in our cohort of infants under 2 years of age.

### Table 2 Estimates of the causal effect using MR compared with multiple regression. The strong difference between estimates from MR and multiple regression analysis (adjusted for measured confounders) for an association between malaria and stunting indicates a high level of unmeasured confounding in the multiple regression analysis

<table>
<thead>
<tr>
<th>Methods</th>
<th>Estimate</th>
<th>P-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR with matching</td>
<td>0.32</td>
<td>0.004</td>
<td>(0.09, 1)</td>
</tr>
<tr>
<td>Multiple Regression</td>
<td>0.02</td>
<td>0.02</td>
<td>(0.003, 0.03)</td>
</tr>
</tbody>
</table>
Our results confirm findings about an association between malaria and stunting from previous studies\(^7\)–\(^9\) as well as findings from earlier studies on an association between mean height-for-age Z-scores and malaria\(^4\)–\(^6\). Previous studies were unable to fully adjust for confounding; a large number of personal characteristics, such as nutritional deficiencies, low socioeconomic status and poor living conditions, are likely to be predictors for both malaria and stunting. Differing levels of confounding in previous studies may have led to findings of no association between malaria and stunting or mean Z-scores\(^10\),\(^12\),\(^13\) or a negative correlation\(^14\) or false conclusions about associations.

In our study, the large difference between the estimate for the effect ratio from the multiple regression and the estimate derived after matching (0.02 vs. 0.32) indicates a substantial level of confounding in the multiple regression. MR takes into account unmeasured confounders that are frequently present in observational studies and are not controlled for in standard regression. Under the assumptions stated in the methods section, MR will control for both unmeasured and measured confounding and provide an unbiased estimate\(^19\),\(^20\),\(^28\). The necessity of these assumptions is a potential limitation that is inherent in our approach. However, we are convinced that the assumptions of an association between HbAS and malaria\(^23\),\(^31\)–\(^34\) and no association between HbAS and stunting other than through malaria\(^39\)–\(^42\) are valid.

Ghanasah et al. have described the HbAS haplotype in a Ghanian population as an extended haplotype of 1.5 Mb containing 25 additional genes.\(^48\) Their analysis shows that this genomic region has a considerable degree of linkage disequilibrium, which potentially could violate our assumption that HbAS is independent of unmeasured confounders. To identify a potential violation, we searched PubMed for reports on associations between stunting or...
malnutrition and any of the other 25 genes on the extended haplotype, including possible alternative gene names, allelic variants and resulting phenotypes, based on searches in the National Center for Biotechnology Information (NCBI) gene database and the Online Mendelian Inheritance in Man database (OMIM) (see Supplementary data Section 2, available at IJE online). These searches did not reveal any reports of an association between genes or genetic variants on the haplotype and stunting. In addition, the sensitivity analysis showed that the estimate of the effect ratio was robust with respect to potential effects by unmeasured confounders. For example, a gene that was in linkage disequilibrium with the sickle cell trait and caused a doubling in odds of inheriting the sickle cell trait would have to at least increase the odds of stunting by a factor of 1.75 to overturn our conclusion. Such an effect of a gene on stunting would be large and surprising. In fact, for any unmeasured confounder to have effects specified in the region above the bolded curve in Figure 2 is very unlikely and, hence, we believe our result is insensitive to unmeasured confounders.

A further limitation to previous studies is potential reverse causality in the association of stunting and malaria. As discussed by Arinaitwe et al, it is difficult to distinguish whether stunting increases the risk of malaria or whether malaria increases the risk of stunting. The MR design of this study solves part of this limitation. It enables us to see whether an increased frequency of malaria causes stunting. Specifically, any association between the sickle cell trait and stunting must come from an effect of malaria on stunting rather than the reverse. The sickle cell trait, which is determined at conception, only affects stunting through its effect on malaria. If malaria did not affect stunting, there would be no association between the sickle cell trait and stunting.

However, there are several additional factors that we cannot analyse or adjust for in our analysis that may have contributed to the differing findings between studies. For example, several studies were of cross-sectional design and looked at a potential association between current malaria and stunting prevalence. Malaria at the time point of the study may or may not correlate to previous exposure. This correlation is likely to differ by transmission intensity of malaria and this varied from low-seasonal to high-perennial transmission. Although the assessment of malaria incidence in the longitudinal studies was probably a more accurate measure of exposure, it seems plausible that the effect of malaria on growth is modulated by immunity and thereby may vary with age. In fact, a study from Tanzania found an effect modification by age with the strongest effect of malaria on stunting in children <1 year of age.

A further potential limitation of our model is the measurement of exposure. We have assumed that the simple sum of malaria episodes over a child’s life is what affects the child being stunted at age 2 years. It may be that a more complex function of a child’s malaria history affects stunting; we plan to investigate this in future work. In addition, the population in this study was enrolled in a clinical trial and seen by medical personnel at close intervals. Prompt medical treatment and nutritional interventions were available free of charge during follow-up. It is possible that the effect of malaria on stunting in this population may differ from that in the general population and especially from that in populations where nutritional deficiencies are more common.

This interpretation of the effect ratio assumes that the effect HbAS has on stunting is solely mediated by a reduction of the number of malaria episodes. However, HbAS also reduces the severity of every malaria episode and the effect on stunting may partly be due to this. This would lead to an over-estimation of the effect that is attributable to each malaria episode. However, the causality conclusion would not change and even the lower boundary of the 95% confidence interval for the effect (0.09) still indicates a substantial effect of malaria on stunting.

Our analysis demonstrates the applicability of HbAS as an instrumental variable for the analysis of conditions related to malaria. As in all observational studies, research on the association of malaria with other medical conditions is often difficult due to the strong influence of confounders and randomized trials are almost always impractical. The method we propose can be applied to reanalyse previous studies in this area, specifically those where the genotyping of the sickle cell gene has already been performed. We hope that our findings will encourage the application of MR to such analyses in the future. A potential further application of MR using HbAS is the elucidation of associations between malaria and other infections. One such analysis was performed by Scott et al, who used MR to analyse an association between malaria and bacteraemia caused by Salmonella spp.

Our analysis provides evidence of a substantial causal effect of malaria episodes on stunting, at least in children <2 years of age in an area of high endemicity. Our findings will hopefully spur further research on this important epidemiological concern in sub-Saharan Africa and increase the application of the sickle cell trait as an instrumental variable in malaria research.

Supplementary Data

Supplementary data is available at IJE online.

Funding

This work was supported by the Bundesministerium für Bildung und Forschung (grant 01KA0202) that funded the original trial, La Roche (Basel,
Switzerland) manufactured study drugs free of charge and Sanofi-Aventis donated Artesunate tablets for treatment of uncomplicated malaria episodes. The German Centre for Infection Research (DZIF) supported B.K. with a clinical leave stipend. The funders had no influence on design or implementation of the study or analysis and interpretation of the data.

Acknowledgements
The authors would like to thank the children that participated in the study and the fieldworkers who contributed to the data collection. We would also like to thank the reviewers for their helpful suggestions to improve the manuscript.

H.K., B.K. and D.S. analysed the results and wrote the manuscript. H.K. and D.S. conducted the statistical analysis. B.K. was involved in the collection of the data. R.K. contributed to the writing of the manuscript and cross-checked the analysis. J.M. and O.A. conducted the original trial and contributed to the writing of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of interest: None declared.

KEY MESSAGES
- Previous association studies between malaria and stunted growth were inconsistent, mainly because of their inability to fully adjust for confounding factors
- In this paper, we use Mendelian randomization and matching to control for both unmeasured and measured confounders where the sickle cell gene was used as the instrument.
- We find a causal relationship, where the risk estimate of stunting increases by 0.32 for every malaria episode.
- A sensitivity analysis shows that our result is reasonably insensitive to violations of Mendelian randomization assumptions.

References