**The effect of malaria on stunting: an instrumental variables approach.**

François Freddy Atebaa,c
Email : ateba.francois\_freddy@courrier.uqam.ca

Seydou Doumbiaa
Email : sdoumbi@icermali.org

Feiko O. ter Kuileb,d
Email: feiko.terkuile@lstmed.ac.uk

Dianne J. Terlouwb,e

Email: Anja.Terlouw@lstmed.ac.uk

Genevieve Lefebvrec

Email : lefebvre.gen@uqam.ca

Simon Kariukid

Email: SKariuki@kemricdc.org

Dylan S. Smallf\*
Email: dsmall@wharton.upenn.edu

aMalaria Research and Training Center & Department of Public Health Education and Research of the Faculty of Medicine and Odonto-Stomatology, University of Sciences, Techniques and Technologies of Bamako, BP 1805 Point G Bamako, Mali.

bLiverpool School of Tropical Medicine, Department of Clinical Sciences, Pembroke Place, Liverpool L3 5QA, UK

cDepartment of Mathematics, University of Quebec at Montreal (UQAM), 201 President-Kennedy Av., Montréal, QC H2X 3Y7 Canada

dCentre of Global Health Research, Kenya Medical Research Institute (KEMRI) Centre for Global Health Research, P.O. Box 1578, 40100 Kisumu, Kenya

eMalawi-Liverpool Wellcome Trust Clinical Research Programme (MLW), P.O. Box 30096 Blantyre, Malawi

fDepartment of Statistics, Wharton School, University of Pennsylvania, 464 Jon M. Huntsman Hall 3730 Walnut Street Philadelphia, PA 19104 Philadelphia, PA, USA.

\* Corresponding author. Tel: +1 (215)-573-5241, E-mail: dsmall@wharton.upenn.edu

Department of Statistics, Wharton School, University of Pennsylvania, Philadelphia, PA, USA.

**Abstract**

**Background:** Previous studies have found mixed evidence for an effect of malaria on stunting, but have suffered from concerns about confounding and/or power. Currently an effect of malaria on stunting is not included in the Lives Saved Tool (LiST) model.

**Methods:** We used instrumental variables regression with the sickle cell trait and random assignment to bed nets as instruments in analysis of data on children 0-2 from a trial in Kenya.

**Results:** We estimate that one additional clinical malaria episode per year approximately doubles the odds of a child being stunted (estimate: 1.99, 95% CI: 1.29, 3.07).

**Conclusions:** Our finding that malaria substantially affects stunting suggests that an effect of malaria on stunting in young children should be considered in the LiST model.

**Keywords:** IV, LiST model,malaria, ITNs.

**Introduction**

In sub-Saharan Africa, 22.2 % of children under five years had stunted growth (low height for age) in 2017 [1]. Children suffering from stunting are at a greater risk of mortality independently from other health conditions [2]. In addition to stunting, sub-Saharan Africa bears the largest burden of malaria morbidity. In spite of this co-occurrence of stunting and malaria, the Lives Saved Tool (LiST), which is widely used to model the impact of policy changes on child mortality in low- and middle-income countries, does not include an effect of malaria on stunting. A recent extended literature review on the effect of malaria on stunting concluded “there is insufficient evidence to include malaria as a determinant of stunting in the LiST model [3],” noting the paucity of the available literature.

Observational studies have found mixed evidence for an effect of malaria on stunting but unmeasured confounding and reverse causality are concerns [3]. A randomized trial in which malaria was randomly assigned would address these concerns but would be unethical. Another way to address concerns about unmeasured confounding is an instrumental variable (IV) approach. An IV is a variable that is associated with an exposure (here malaria) but only affects the outcome (here stunting) through its association with the exposure and is independent of the unmeasured confounders. IV approaches can be used to extract a confounder-free comparison between exposure groups from a confounded study [4,5], enabling valid estimation of causal effects. One potential IV for the effect of malaria on stunting is a randomized intervention intended to reduce malaria. Although such randomized interventions have not previously been directly used as IVs, the effect of such randomized interventions on stunting has been examined and the interventions have not been associated with statistically significant reductions in stunting [3]. However, variations in effect by age as well as power are a concern, especially with interventions that do not have a large effect on malaria [3]. Another potential IV for the effect of malaria on stunting is a genetic trait which affects the risk of malaria but does not affect the risk of stunting in ways other than through its effect of malaria. The use of genetic traits as IVs is called Mendelian randomization [6]. Kang et al [7,8] used the sickle cell trait as an IV and found evidence that malaria is a major cause of stunting. Kang et al. noted that their study may be limited in generalizability because it is based on data from a study in one region, the Ashanti region in Ghana, and it would be desirable to replicate the study in different regions.

The power of an IV study can be increased by using multiple IVs. Here we address some of the limitations of previous studies of the effect of malaria on stunting by using two IVs, a randomized bednet intervention and the sickle cell trait, in a secondary analysis of a bednet intervention randomized clinical trial in Western Kenya [9].

**Materials and methods.**

We use data from the Asembo Bay Cohort study, a longitudinal observational study of a cohort of children in an area of intense perennial of malaria transmission in Western Kenya from 1993-1996 that was followed in 1997-1999 by a cluster randomized trial (with the clusters being 19 villages) of insecticide-treated bednets (ITNs) [9–11]. The observations in our study are scheduled monthly visits at which blood smears to assess malaria parasite density and anthropometric measurements were taken. Children were followed for clinical malaria between the monthly visits through biweekly weekly visits to take a child’s temperature and assess symptoms as well as unscheduled visits – caretakers were encouraged to contact the village health workers who were employed by the study if the child was ill in between scheduled visits (village-based care provided by the study was free). If a child was ill or had a history of fever in between the bi-weekly visits, a blood smear to assess malaria parasite density was taken. See [9] for details on the data collection procedure. For this analysis, we included observations of children when they were less than two years old, which reflected the age group at the highest risk of malaria morbidity at the time [9]. We considered the effect of the child’s clinical malaria incidence rate (per year lived) on the outcome of whether or not the child is stunted (height for age Z-score less than -2). Z-scores were calculated using Epi-Info version 2000 (Centers for Disease Control and Prevention, Atlanta, GA). A clinical malaria episode was defined as an axillary body-temperature of ≥37.5°C with malaria parasitemia of any density confirmed by microscopy [9].

To control for potential unmeasured confounding, we used an IV approach. We used two IVs, (i) the proportion of a child’s life when he/ she was in the randomized bednet intervention group (e.g., 0 for child in village randomized to control in the bednet trial, 0.5 for 1-year old child whose village was randomized to intervention in the bednet trial where the intervention started when the child was six months old) and (ii) whether the child had the sickle cell trait. Figure 1 is a causal graph that depicts the assumptions that the proportion of a child’s life in the bednet intervention group and the sickle cell trait are valid IVs. The proportion of a child’s life in the bednet intervention group is plausibly a valid IV because the bednet intervention had a strong effect on reducing malaria [9] and the randomization makes it independent of unmeasured confounders (Note that in order for proportion of a child’s life in the bednet intervention to be a valid IV, it needs only be associated with proper bednet usage and correspondingly malaria episodes [12]. It does not need to be a perfect predictor of proper bednet usage or malaria episodes, although the stronger a predictor it is, the more powerful the study will be [4]. In fact, about 72% of children assigned to the bednet intervention group used the net per guidelines Usage of privately owned bednets by those not assigned to the bednet intervention group was rare prior to the start of the cluster randomized trial in 1997 but increased during the trial). The sickle cell trait is plausibly a valid IV because it protects against malaria [13], is randomly assigned conditional on parents’ genotype and is not thought to affect height except through malaria [7]. Support for the sickle cell trait not affecting height except through malaria is provided by studies among African American, Dominican and Jamaican children – populations in which the sickle cell trait is common but who live in non-malaria-endemic areas – that have found no evidence of differences in physical development between children with the sickle cell trait and children without the sickle cell trait or sickle cell disease [7,14–17]).

To estimate the causal effect of malaria on stunting, we used two-stage residual inclusion IV regression where we included as covariates the child’s age and the year of observation to account for age effects and secular trends respectively as well as indicator variables for the child’s village to account for clustering by village [18–20]. In the first stage of two-stage residual inclusion IV regression, the predicted exposure for each observation, given the observation’s IVs and covariates, is computed using linear regression and then in the second stage, a multivariable logistic regression of the outcome on the exposure, the residual from the first stage regression and the covariates is computed [18]:



where is the clinical malaria incidence rate of child *i* at time where child *i* is observed at times with the observation times vary from child to child, is the proportion of child *i*’s life spent in the randomized bednet intervention group at time , is an indicator variable for whether child *i* has the sickle cell trait (genotype HbAS), is child *i*’s age in months at time , is the village child *i* lives in (villages numbered 1,…,19), is the year corresponding to time , is the residual from the linear regression of on and is an indicator variable for whether child *i* is stunted at time . For valid IVs, the residual of the first stage regression “intercepts” the effect of unmeasured confounders [19]. We used the bootstrap to obtain confidence intervals and p-values [21]. In the bootstrap, we resampled children, including all a child’s observations if the child was resampled; this bootstrap accounts for the effect of repeated observations of a child on standard errors [22]. A p-value <0.05 was considered statistically significant. To measure whether the IVs are weak, we computed the partial F statistic for the IV in the first stage regression of the exposure on the IVs and covariates; for two IVs, a partial F statistic below 11.6 indicates the IVs are weak [23]. We excluded children with sickle cell disease and those for which any of the covariates or IVs were missing. In addition to considering all the observations from ages 0-23 months, we did subset analyses of the observations between 0-11 months and between 12-23 months.

**Results and Discussion**

Our analysis included 1800 children of which 363 (20.2%) had the sickle cell trait, and included 19,369 child observations. 5327 child observations were excluded because of missing covariates or IVs. For the most part, the missingness was due to the sickle cell trait being missing (4743 observations). Of the observations with the sickle cell trait not missing, the percentage excluded because of other missing covariates or IVs among those with the sickle cell trait vs. without was similar (3.7% vs. 3.6%). The proportion with missing covariates or IVs among those with positive time under bednet randomization is higher than among those with zero time under bednet randomization (33.6% vs. 17.2%). The mean number of observations in our analysis per child was 10.8 and the standard deviation was 6.8; the five number summary was min=1, 25th percentile = 5, median = 10, 75th percentile = 17, max= 26. The mean number of observations per child was similar among children with the sickle cell trait vs. those without (10.9 vs. 10.7). It was lower among children assigned to the bednet intervention at some point vs. those not (9.3 vs. 11.2) as children who turned two prior to the start of the cluster randomized trial (who were perforce not assigned to the bednet intervention) had complete follow up to age two whereas some children in the cluster randomized trial had incomplete follow up because they turned two when the study ended in 1999. Children were stunted at 6082 (31.4%) of the observations; 61.9% (1114) of the 1800 children in the analysis were stunted for at least one observation. Of these 19,369 observations, 11,888 (61.4%) were from 0-11 months old children and 7481 (38.6%) from 12-23 months old children. The lower number of observations from 12-23 months old children was related to some children being born not in time to reach 12-23 months by the end of the study, some children dying at a young age and some children being lost to follow up [9]. The first stage partial F statistics for the IVs were 130.9 for 0-23 months, 69.6 for the 0-11 months and 81.6 for the 12-23 months old children, indicating that the IVs are not weak.

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Table 1**

|  |
| --- |
| Effect of increase in clinical malaria incidence rate by 1 on odds of being stunted |
|  | Estimateof Odds Ratio 95% CI p-value |
| 0-23 months | 1.99 | (1.11, 3.58) |  0.0213  |
|  |  |  |  |
|  |  |  |  |
| 0-11 months | 2.13 | (1.18, 3.85) | 0.0123 |
|  |  |  |  |
|  |  |  |  |
| 12-23 months | 1.82 | (1.01, 3.27) | 0.0457 |

**Table 1.** Instrumental variable analysis of the effect of an increase in the clinical malaria incidence rate (per year) of 1 on the odds of a child being stunted.

For example an estimate of 2 would mean that the odds of being stunted would be multiplied by 2 if the child had an additional malaria episode per year.

Note: the models were adjusted for age in month and study year,in all the age ranges both age and study year were significant (p-value < 0.05).

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Table 1 shows the results of our IV analysis. We find evidence that malaria causes a substantial increase in the odds of being stunted. For children 0-23 months, one additional malaria episode per year is estimated to approximately double the odds of being stunted (odds ratio estimate 1.99; 95% confidence interval [CI]: [1.11, 3.58], P=0.02). Strengths of our study include that by combining the sickle cell trait IV approach with a large randomized trial where the intervention (bed nets) had a substantial effect on reducing clinical malaria (by an estimated 52%) [9], we increased power compared to previous studies of the effect of malaria on stunting that have used either the sickle cell trait IV alone or looked at the effect of a randomized intervention on stunting alone.[[1]](#footnote-1) A limitation is that our inferences assume that the randomized bednet treatment and the sickle cell trait are valid IVs; however, these assumptions are plausible [7]. Other limitations include that the population in this study was enrolled in a clinical trial and seen by medical personnel at two-weekly intervals with prompt medical treatment available free of charge. The effect of malaria on stunting in this population may, therefore, differ from that in the general population where prompt medical treatment may be lacking. Our analysis accounted for correlation among children within the same village by including an indicator variable for each village but did not account for further spatial correlation within a village. However, even if malaria and stunting are correlated within a village, as long as the sickle cell trait is not correlated within a village, the standard errors we estimated by resampling children will not be biased; if the sickle cell trait and stunting are both positively correlated within a village, then the standard errors would be underestimated [24].

Our study does not address whether malaria is a direct proximate cause of stunting or whether it is mediated by other causes such as nutritional deficiencies or disruption of iron status, nor does it address the time course by which malaria could affect stunting. These would be good topics for future research.

**Conclusion**

Our finding of a substantial effect of malaria on stunting suggests that an effect of malaria on stunting in young children should be considered in the LiST model.

Authors’ statements

**Authors’ contributions**

 FA, DS,SK,AT,FTK,GL and SD contributed to study design,writing of the manuscript and data analysis.

**Acknowledgments**

We would like to thank the Fogarty International Center of the National Institutes of Health of the United States for supporting Francois Ateba under Grant D43TW008652 and the West African International Center of Excellence in Malaria Research (ICEMR) grant U19 AI 089696 and U19 AI 129387 for supporting his works related to his grant.

**Competing Interests**

The authors declare no conflicts of interests.

**Ethical approval**

The ITN study and the Asembo Bay Cohort Project were approved by the institutional review boards of the Kenya Medical Research Institute (Nairobi, Kenya) and the Centers for Disease Control and Prevention (Atlanta,GA). Informed consent was obtained from all caretakers after explanation of the study procedures in the local language.

**References**

1. *2018 Global Nutrition Report - Global Nutrition Report*;

2. Chataut, J.; Khanal, K. Assessment of nutritional status of children under five years of age in rural Nepal. *Kathmandu Univ. Med. J.* **2016**.

3. Jackson, B.D.; Black, R.E. A Literature Review of the Effect of Malaria on Stunting. *J. Nutr.* **2017**, jn242289, doi:10.3945/jn.116.242289.

4. Baiocchi, M.; Cheng, J.; Small, D.S. Instrumental variable methods for causal inference. *Stat. Med.* **2014**, *33*, 2297–2340, doi:10.1002/sim.6128.

5. Angrist, J.D.; Pischke, J.S. *Mostly harmless econometrics: An empiricist’s companion*; 2008; ISBN 9780691120348.

6. Smith, G.D.; Ebrahim, S. *International Journal of Epidemiology*. 2003, pp. 1–22.

7. Kang, H.; Kreuels, B.; Adjei, O.; Krumkamp, R.; May, J.; Small, D.S. The causal effect of malaria on stunting: A Mendelian randomization and matching approach. *Int. J. Epidemiol.* **2013**, *42*, 1390–1398, doi:10.1093/ije/dyt116.

8. Kang, H.; Kreuels, B.; May, J.; Small, D.S. Full matching approach to instrumental variables estimation with application to the effect of malaria on stunting. *Ann. Appl. Stat.* **2016**, *10*, 335–364, doi:10.1214/15-AOAS894.

9. ter Kuile, F.O.; Terlouw, D.J.; Kariuki, S.K.; Phillips-Howard, P.A.; Mirel, L.B.; Hawley, W.A.; Friedman, J.F.; Shi, Y.P.; Kolczak, M.S.; Lal, A.A.; et al. Impact of permethrin-treated bed nets on malaria, anemia, and growth in infants in an area of intense perennial malaria transmission in western Kenya. *Am. J. Trop. Med. Hyg.* **2003**, *68*, 68–77.

10. Bloland, P.B.; Ruebush, T.K.; McCormick, J.B.; Ayisi, J.; Boriga, D.A.; Oloo, A.J.; Beach, R.; Hawley, W.; Lal, A.; Nahlen, B.; et al. Longitudinal cohort study of the epidemiology of malaria infections in an area of intense malaria transmission I. Description of study site, general methodology, and study population. *Am. J. Trop. Med. Hyg.* **1999**, *60*, 635–640, doi:10.4269/ajtmh.1999.60.635.

11. Phillips-Howard, P.A.; Nahlen, B.L.; Alaii, J.A.; ter Kuile, F.O.; Gimnig, J.E.; Terlouw, D.J.; Kachur, S.P.; Hightower, A.W.; Lal, A.A.; Schoute, E.; et al. The efficacy of permethrin-treated bed nets on child mortality and morbidity in western Kenya I. Development of infrastructure and description of study site. *Am. J. Trop. Med. Hyg.* **2003**, *68*, 3–9.

12. Hernán, M.A.; Robins, J.M. Instruments for causal inference: An epidemiologist’s dream? *Epidemiology* **2006**, doi:10.1097/01.ede.0000222409.00878.37.

13. Taylor, S.M.; Parobek, C.M.; Fairhurst, R.M. Haemoglobinopathies and the clinical epidemiology of malaria: A systematic review and meta-analysis. *Lancet Infect. Dis.* **2012**, doi:10.1016/S1473-3099(12)70055-5.

14. Kramer, M.S.; Rooks, Y.; Pearson, H.A. Growth and Development in Children with Sickle-Cell Trait: A Prospective Study of Matched Pairs. *N. Engl. J. Med.* **1978**, *299*, 686–689, doi:10.1056/NEJM197809282991303.

15. Rehan, N. Growth status of children with and without sickle cell trait. *Clin. Pediatr. (Phila).* **1981**, *20*, 705–9, doi:10.1177/000992288102001103.

16. Ashcroft MT, Desai P, R.S. Growth, behavior, and educational achievement of Jamaican children with sickle-cell trait. *, Br Med J* **1976**, *6022*, 1371–73.

17. Ashcroft MT, Desai P, Grell GA, S.B. Heights and weights of West Indian children with the sickle cell trait, Arch Dis Child. *Arch Dis Child* **1978**, *53*, 596–98.

18. Terza, J. V.; Basu, A.; Rathouz, P.J. Two-stage residual inclusion estimation: Addressing endogeneity in health econometric modeling. *J. Health Econ.* **2008**, doi:10.1016/j.jhealeco.2007.09.009.

19. Nagelkerke, N.; Fidler, V.; Bernsen, R.; Borgdorff, M. Estimating treatment effects in randomized clinical trials in the presence of non-compliance. *Stat. Med.* 2000.

20. Koladjo, B.F.; Escolano, S.; Tubert-Bitter, P. Instrumental variable analysis in the context of dichotomous outcome and exposure with a numerical experiment in pharmacoepidemiology. *BMC Med. Res. Methodol.* **2018**, doi:10.1186/s12874-018-0513-y.

21. Efron, B.; Tibshirani, R.J. *An Introduction to the Bootstrap*; 1993;

22. Field, C.A.; Welsh, A.H. Bootstrapping clustered data. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **2007**, doi:10.1111/j.1467-9868.2007.00593.x.

23. Stock, J.; Yogo, M.; Wright, J. A Survey of Weak Instruments and Weak Identification in Generalized Method of Moments. *J. Bus. Econ. Stat.* **2002**, *20*.

24. Shore-Sheppard, L. *The precision of instrumental variables estimates with grouped data*; Industrial Relations Section Working Papers; 1996;

25. Greevy, R.; Silber, J.H.; Cnaan, A.; Rosenbaum, P.R. Randomization inference with imperfect compliance in the ace-inhibitor after anthracycline randomized trial. *J. Am. Stat. Assoc.* **2004**, *99*, 7–15, doi:10.1198/016214504000000025.

Figure 1: Causal graph depicting the assumptions that the proportion of child’s life in the randomized bednet intervention group and the sickle cell trait are instrumental variables for the effect of malaria on stunted growth. The graph is meant to depict relationships within strata of measured confounders (child’s age, year of observation and village). The key assumptions are that (i) proportion of child’s life in bednet group and the sickle trait are independent of unmeasured confounders (absensce of line between proportion of child’s life in bednet group/sickle cell trait and unmeasured confounders) and (ii) proportion of child’s life in bednet group and the sickle cell trait have no direct effect on stunted growth (absence of line between proportion of child’s life in bednet group/sickle cell trait and stunted growth).



1. We are not aware of previous studies that have used a randomized intervention as an IV; however, the p-value for a test of no effect of malaria on stunting when a randomized intervention is used as an IV is the same as the p-value for a test of no effect of the randomized intervention on stunting [25]. Previous studies which have examined whether a randomized intervention to prevent malaria has prevented stunting have not found a significant effect [3]. [↑](#footnote-ref-1)