Title: Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis

More details/abstract: Background: Future progress in tacking malaria mortality will probably be hampered by the development of resistance to drugs and insecticides and by the contraction of aid budgets. Historically, control was often achieved without malaria specific interventions. Our aim was to assess whether socioeconomic development can contribute to malaria control. Methods: We did a systematic review and meta-analysis to assess whether the risk of malaria in children aged 0–15 years is associated with socioeconomic status. We searched Medline, Web of Science, Embase, the Cochrane Database of Systematic Reviews, the Campbell Library, the Centre for Reviews and Dissemination, Health Systems Evidence, and the Evidence for Policy and Practice Information and Co-ordinating Centre evidence library for studies published in English between Jan 1, 1980, and July 12, 2011, that measured socioeconomic status and parasitologically confirmed malaria or clinical malaria in children. Unadjusted and adjusted effect estimates were combined in fixed effects and random-effects meta-analyses, with a subgroup analysis for different measures of socioeconomic status. We used funnel plots and Egger's linear regression to test for publication bias. Findings: Of 4696 studies reviewed, 20 met the criteria for inclusion in the qualitative analysis, and 15 of these reported the necessary data for inclusion in the meta-analysis. The odds of malaria infection were higher in the poorest children than in the least poor children (unadjusted odds ratio [OR] 1·66, 95% CI 1·35–2·05, p<0·001, I²=68%; adjusted OR 2·06, 1·42–2·97, p<0·001, I²=63%), an effect that was consistent across subgroups. Interpretation: Although we would not recommend discontinuation of existing malaria control efforts, we believe that increased investment in interventions to support socioeconomic development is warranted, since such interventions could prove highly effective and sustainable against malaria in the long term.

Version: Accepted Author Manuscript

Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis

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Summary

Background Future progress in tacking malaria mortality will probably be hampered by the development of resistance to drugs and insecticides and by the contraction of aid budgets. Historically, control was often achieved without malaria-specific interventions. Our aim was to assess whether socioeconomic development can contribute to malaria control.

Methods We did a systematic review and meta-analysis to assess whether the risk of malaria in children aged 0–15 years is associated with socioeconomic status. We searched Medline, Web of Science, Embase, the Cochrane Database of Systematic Reviews, the Campbell Library, the Centre for Reviews and Dissemination, Health Systems Evidence, and the Evidence for Policy and Practice Information and Co-ordinating Centre evidence library for studies published in English between Jan 1, 1980, and July 12, 2011, that measured socioeconomic status and parasitologically confirmed malaria or clinical malaria in children. Unadjusted and adjusted effect estimates were combined in fixed-effects and random-effects meta-analyses, with a subgroup analysis for different measures of socioeconomic status. We used funnel plots and Egger's linear regression to test for publication bias.

Findings Of 4696 studies reviewed, 20 met the criteria for inclusion in the qualitative analysis, and 15 of these reported the necessary data for inclusion in the meta-analysis. The odds of malaria infection were higher in the poorest children than in the least poor children (unadjusted odds ratio [OR] 1·66, 95% CI 1·35–2·05, p<0·001, I^2=68%; adjusted OR 2·06, 1·42–2·97, p<0·001, I^2=63%), an effect that was consistent across subgroups.

Interpretation Although we would not recommend discontinuation of existing malaria control efforts, we believe that increased investment in interventions to support socioeconomic development is warranted, since such interventions could prove highly effective and sustainable against malaria in the long term.

Introduction

Malaria remains one of the most serious public health problems worldwide, with 2·57 billion people at risk of falciparum malaria in 2010.[1] Although the burden of malaria[A: addition ok? Or malaria incidence, or malaria prevalence?] is falling globally, morbidity and mortality remain high, with estimates of total reported deaths in 2010 between 655 000[2] and 1·24 million,[3] with an estimated 39·97 million disability-adjusted life years lost in 2000[A: could this figure be updated with data from GBD 2010? (*Lancet* 2012; 380: 2197–223)].[4] In addition to direct health effects, malaria also has a serious negative effect on socioeconomic development, and indeed "where malaria prospers most, human societies have prospered least".[5] This effect is shown by the relation between an index of income and education[6] and the cumulative probability of malaria deaths in 43 African countries[3] in children aged 0–5 years (figure 1) and in all age groups[A: do you mean children of all age groups (if so, up to what age?), or is this inclusive of adults? Could this data be added to the appendix as a supplementary figure? Or even to replace figure 1, if this latter estimate better matches your study population (age 0–15 years)?] (R^2=0·256, p=0·001) in 2010 (appendix p 1).

Costs associated with the burden of malaria constitute 5·8% of the total gross domestic product of sub-Saharan African (roughly US$12 billion annually).[7] Both national income[8] and rates of economic growth[5] are lower in malaria-endemic countries than in countries where the disease is not endemic. One estimate[8] suggests that a 10% reduction in malaria is associated with 0·3% increased growth, and other research has shown similar effect sizes[A: sentence correct as edited?].[9] Indeed, these findings, together with others for HIV/AIDS, provided the impetus for the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria.[7] Malaria control and elimination is therefore seen as integral to the economic prosperity of malaria-endemic countries.[10] This worldwide recognition also ensured that malaria was the focus of one of the Millennium Development Goals.[11]

However, efforts to control malaria are almost always focused on reduction of the disease through interventions that are derived solely from the health sector and are suitable for rapid and massive scale-up. Long-lasting insecticidal nets (LLINs) and indoor residual spraying are both highly efficient methods of reducing transmission quickly and, combined with artemisinin-based combination therapy, are undoubtedly a major reason for the reduction in the malaria burden[A: addition correct? Or incidence/prevalence?] in sub-Saharan African.[12] However, such strong pressure on vector and parasite populations will inevitably lead to the selection and

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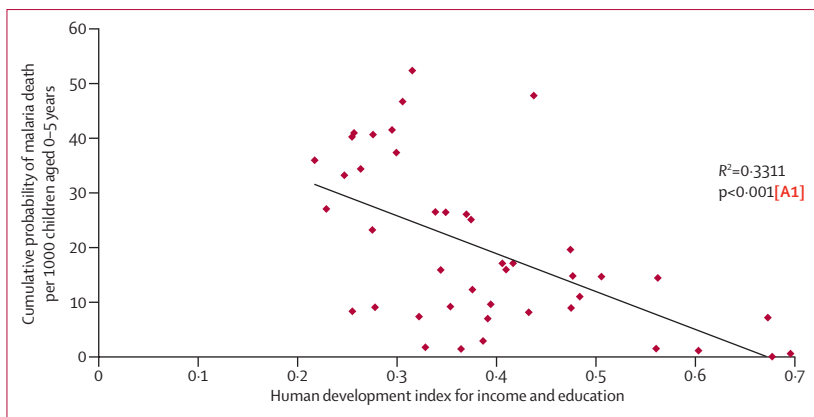
See **Online** for appendix

Figure 1: Malaria burden and human development index for income and education in 43 countries in sub-Saharan Africa

Data for cumulative probability of malaria death per 1000 children aged 0–5 years are for 2010 and were taken from Murray and colleagues.[3] Our human development index for income and education is for 2011 and was calculated from the UN Development Programme website[6] and was derived from three variables: gross national income per head in purchasing power parity terms for 2011 (constant international 2005 [A: US?]\$); expected years of schooling for children as of 2011; and mean years of schooling for adults as of 2011. Methods for the calculation are shown in the appendix (p 1).[6] All 43 countries in sub-Saharan Africa for which data for both variables were available were included.[A1: please report exact p value unless is <0·0001 (not <0·001)]
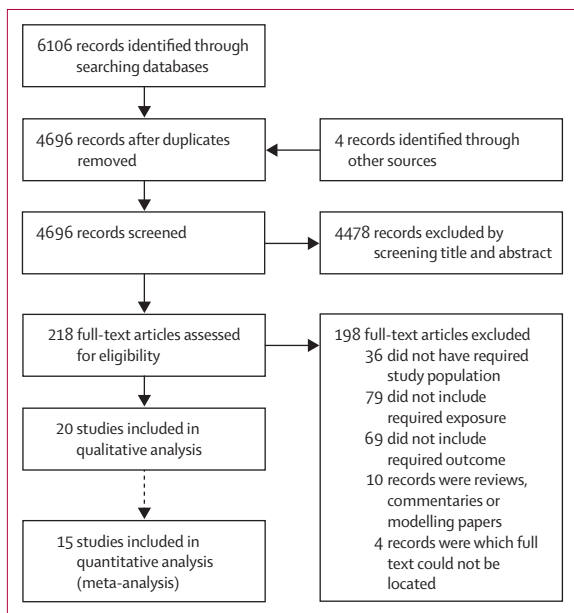

Figure 2: Study selection

spread of resistant strains of mosquitoes and malaria parasites, respectively. Resistance to artemisinins, which has emerged in malaria parasites in southeast Asia,[13] will probably spread globally. Resistance to all four classes of insecticide available for indoor residual spraying (including the pyrethroids, the only insecticides currently available for impregnation of bednets), has now been documented in sub-Saharan African.[14]

The honeymoon period for malaria control is threatened both by resistance and, in the wake of the recent economic crisis, by so-called donor fatigue,

creating a serious risk of a resurgence of malaria, as has occurred repeatedly in the past.[15] Other interventions must be considered, as is recognised in the integrated vector management strategies supported by WHO,[16] which, through combining efforts to control several vector-borne diseases, can yield sustainable and cost-effective reductions in the transmission of malaria, lymphatic filariasis, dengue, and other diseases.[17]

However, since malaria control in many countries has historically been achieved without such malaria-specific interventions, socioeconomic development could potentially provide an effective and sustainable means of control in malaria-endemic countries. Based on this hypothesis, we did a systematic review and meta-analysis of the evidence for the relation between risk of malaria infection and socioeconomic status in children aged 0–15 years.[A: some text removed because belonged in either Methods, Results, or Discussion]

Methods

Search strategy and eligibility criteria

We followed recommendations made by the Meta-analysis of Observational Studies in Epidemiology[18] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses groups.[19] We searched Medline, Web of Science, Embase, the Cochrane Database of Systematic Reviews, the Campbell Library, the Centre for Reviews and Dissemination, Health Systems Evidence, and the Evidence for Policy and Practice Information and Co-ordinating Centre evidence library to identify studies published in English between Jan 1, 1980, and July 12, 2011. We selected synonymous terms and used these to develop the search strategy (appendix pp 2–3). Bibliographies of relevant studies retrieved from the searches were checked for additional publications. The search strategy was not limited by study design. We excluded reports published before 1980, since we sought to examine evidence from the period most applicable to the present status of malaria control.

Studies retrieved were eligible for inclusion if they satisfied all our criteria: the study population consisted of children aged 0–15 years; the association between socioeconomic status and malaria was assessed; and the outcome of interest was prevalence of microscopically confirmed or rapid diagnostic test-confirmed *Plasmodium falciparum* infection or clinical malaria (fever and *P falciparum* infection). Low socioeconomic status was defined as not owning defined household assets; a low household income; a low score in an asset-based index of socioeconomic status, constructed with principal components or factor analysis; or parents having an unskilled rather than a skilled occupation. Cross-sectional, case-control, and cohort studies were all included in the analysis. Studies with low response rates were included. Only studies done in local populations of countries classified as malaria-endemic[20] were included, and studies with populations of migrants, displaced

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	Study site	Study design	n	Participants	Recruitment of participants	Exposure	Outcome	Control group [A: ok?]	Measure of effect	Un-adjusted effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quan-titative analysis
Studies included in the meta-analysis													
Al-Taiar et al,[23] 2009	Yemen	Case-control	628	Aged 6 months to 10 years	Recruited from health centres	Low vs high socioeconomic status	Clinical malaria (parasitaemia plus fever)	Age-matched, healthy, community controls	OR	1·76 (1·21–2·57)	NA	NA	NA
Baragatti et al,[24] 2009	Burkina Faso	Cross-sectional	3354	Aged 6 months to 12 years	Randomly sampled from community	Family has irregular land tenure vs regular land tenure	PfPR	None	OR	2·07 (1·10–3·88)	1·85 (1·17–2·92)	Age, land tenure, building density, equipment, education, bednet use, and season	NA
Clarke et al,[25] 2001	The Gambia	Cross-sectional	1196	Aged 6 months to 5 years	Cluster-sampled from 48 villages	"Poor" vs "less poor"[A: direct quotes?]	PfPR	None	OR	2·34 (1·35–4·05)	NA	NA	NA
Custodio et al,[26] 2009	Equatorial Guinea	Cross-sectional	552	Aged 0–5 years	Randomly sampled from community	Low vs high socioeconomic status	PfPR	None	OR	1·49 (0·98–2·25)	NA	NA	NA
Gahutu et al,[27] 2011	Rwanda	Cross-sectional	749	Aged 0–5 years	Randomly selected from villages, health centre, and district hospital	Low household income (<5000 Rwandan francs) vs high income (≥5000 Rwandan francs)	PfPR	None	OR	1·59 (1·05–2·40)	NA	NA	NA
Ghebreyseus et al,[28] 2000	Ethiopia	Cross-sectional	2114	Aged 0–10 years	Randomly sampled from community	House does not own a radio vs household owns a radio	Incidence of clinical malaria (parasitaemia plus fever) [A2]	None	OR	0·97 (0·60–1·59)	NA	NA	NA
Koram et al,[29] 1995	The Gambia	Case-control	768	Aged 3 months to 10 years	Recruited from three health centres	Family does not own a refrigerator vs family owns a refrigerator	Clinical malaria (parasitaemia plus fever)	Healthy controls matched by age, date [A:date of what?], and neighbour-hood	OR	2·30 (1·44–3·75)	2·58 (1·46–4·45)	Place of residence, travel history, ownership of housing plot, house type, crowding, mother's knowledge of malaria, insecticide use, and medicine use	NA
Krefis et al,[30] 2010	Ghana	Cross-sectional	1496	Aged less than 15 years	Recruited when visiting major hospital for medical care	Low vs high socioeconomic status	Clinical malaria (parasitaemia plus fever)	None	OR	NA	1·79 (1·32–2·44)	Age, sex, ethnicity, number of children in family, mother's age, and place of residence	NA

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	Study site	Study design	n	Participants	Recruitment of participants	Exposure	Outcome	Control group [A: ok?]	Measure of effect	Un-adjusted effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quan-titative analysis
(Continued from prevous page)													
Ong'Echa et al,[31] 2006	Kenya	Case control	374	Aged 0–3 years (children with cerebral malaria and those with previous hospital visits were excluded)	Recruited when visiting district hospital with symptoms of malaria	Parents are farmers vs parents are not farmers	Clinical malaria (para-sitaemia plus fever)	Healthy controls recruited from MCH[A: what is MCH?] clinic	OR	3·85 (1·64–9·09)	0·92 (0·41–2·04)	Child risk factors[A: what are these?], nutritional factors, house type, and mosquito control measures	NA
Pullan et al,[32] 2010	Uganda	Cross-sectional	1770	Aged 5–15 years	Selected from all households in district	Lowest vs highest socio-economic status quintile	PfPR	None	OR	1·25 (0·74–2·13)	NA	NA	NA
Ronald et al,[33] 2006 (1)[A1]	Ghana	Cross-sectional	296	Aged 1–9 years	Randomly sampled from community	Decreasing household socio-economic status	PfPR	None	OR	3·22 (1·95–5·32)	3·95 (2·26–6·90)	Age and travel to rural areas	NA
Slutsker et al,[34] 1996	Malawi	Cross-sectional	3915	Aged 0–3 months	Infants' mothers were enrolled into a chemo-prophylaxis study at four antenatal clinics	Low vs high or medium socio-economic status	PfPR	None	OR	1·80 (1·30–2·10)	NA	NA	NA
Villamor et al,[35] 2003	Tanzania	Cross-sectional	687	Aged 6–60 months	Children were enrolled in a vitamin A supple-mentation trial when admitted to hospital with pneumonia	No electricity at home vs electricity at home	PfPR	None	OR	1·84 (1·23–2·76)	NA	NA	NA
Winskill et al,[36] 2011 (1)[A1]	Tanzania	Cross-sectional	1438	Aged 6 months to 13 years	Randomly selected from 21 hamlets	Decreasing household socioeconomic status	PfPR	None	OR	1·15 (0·94–1·39)	NA	NA	NA
Yamamoto et al,[37] 2010	Burkina Faso	Case-control	283	Aged 0–9 years	Recruited by passive case detection at central laboratory	Low vs high socioeconomic status	Clinical malaria (para-sitaemia plus fever)	Controls from demographic surveillance system database matched for age, sex, ethnicity, and residence	OR	0·47 (0·20–1·08)	NA	NA	NA
Studies included in the qualitative analysis, but excluded from the meta-analysis													
Clark et al,[38] 2008	Uganda	Cohort	558	Aged 1–10 years	Recruited from a census population in one parish	1st and 2nd (lowest) vs 4th wealth quintile (highest)	Incidence of clinical episodes of malaria per person-year at risk	None	RR	2·04 (1·54–2·70)	1·30 (0·96–1·79)	Age, sickle cell trait, G6PD deficiency in girls, bednet use, household crowding, and distance from swamp	Not possible to calculate OR
													(Continues on next page)

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	Study site	Study design	n	Participants	Recruitment of participants	Exposure	Outcome	Control group [A: ok?]	Measure of effect	Un-adjusted effect (95% CI)	Adjusted effect (95% CI)	Factors adjusted for	Reason for exclusion from quan-titative analysis
(Continued from prevous page)													
Klinkenberg et al,[39] 2006	Ghana	Cross-sectional	1744	Aged 6–60 months	Randomly sampled from communities near (<1000 m) and less near (>1000 m) agricultural sites in Accra	Socio-economic status is below mean for the city[A: vs?]	PfPR	None	In-sufficient in-formation provided	NA	NA	NA	Not possible to calculate OR
Kreuels et al,[40] 2008	Ghana	Cohort	535	Aged 2–4 months	Recruited from nine villages after visiting health centre (children with chronic diseases excluded)[A: correct as edited?]; followed up for 24 months[A: correct as edited? Is this relevant to recruitment procedure?]	Family does not have good financial situation vs family has good financial situation	Clinical malaria (parasitaemia plus fever)	None	Incidence rate ratio	1·59 (1·33–1·89)	1·52 (1·27–1·82)	Sex, ethnicity, season of birth[A: correct?], sickle cell trait, mother's education, mother's occupation, knowledge of malaria, and protective measures	Not possible to calculate OR
Matthys et al,[41] 2006 (2)[A1]	Côte d'Ivoire	Cross-sectional	672	Aged 0–15 years	Selected from farming and non-farming households	Low vs high socioeconomic status	PfPR	None	OR	NA	2·44 (0·88–10·00)	Age, agricultural zone, crops grown, irrigation, overnight stays in temporary farm huts[A: correct?], and distance to permanent ponds and fish ponds	Bayesian credible intervals reported only
Pullan et al,[42] 2010 (1)(2)[A1]	Uganda	Cross-sectional	1844	Aged 5–15 years	All residents of four villages asked to participate, with 78% successfully enrolled[A: correct?]	Decreasing household socioeconomic status	PfPR	None	OR	NA	2·27 (0·88–25·00)	Age, bednet use	Bayesian credible intervals reported only

[A1: what are these numbers in brackets?] [A2: why does this outcome say "incidence of clinical malaria" when the others just say "clinical malaria"? Please add what measure of clinical malaria is used in all the other studies] OR=odds ratio. PfPR=*Plasmodium falciparum* parasite rate. RR=relative risk.

Table: Studies included in the systematic review and meta-analysis

people, or military personnel were excluded. Studies in which the outcome was severe malaria, congenital malaria, or in which most infections were not *P falciparum* were also excluded.

Data extraction

We first screened titles and abstracts, and then one reviewer (LST) screened the relevant full-text articles. SWL also reviewed 22 (10%) of the full-text articles screened, with any discrepancies resolved by RS[A: what was the basis for selecting these 22 for secondary review?]. One reviewer (LST) extracted study characteristics and unadjusted and adjusted effect sizes with 95% CIs and recorded the data in a standard form. We did quality and risk-of-bias assessments as recommended by Wells and colleagues[A: correct?].[21]

Statistical analysis

Studies that met the eligibility criteria and that reported unadjusted or adjusted odds ratios (ORs) with 95% CIs, or presented sufficient data for the calculation of unadjusted ORs and 95% CIs, were included in the meta-analysis. We used the generic inverse-variance method for the meta-analysis, in which weight is given to each study according to the inverse of the variance of the effect, to minimise uncertainty about the pooled effect estimates. Both outcomes (*P falciparum* infection and clinical malaria) were combined in the analysis. We allocated the included studies into four subgroups, according to the measure of socioeconomic status used: asset ownership; household wealth; socioeconomic index; or parents' occupations. We did separate analyses for unadjusted and adjusted ORs. Missing data were not problematic since meta-regression of individual data was not done.

Initially we did a fixed-effects meta-analysis, but if I^2 was large (>50%), which suggests substantial heterogeneity between studies, we used random-effects analysis[A: sentence correct as reworded?]. Random-effects analysis adjusts the standard errors of each study estimate of effect to include a measure of variation in the effects reported between studies. We produced forest plots to visually assess the ORs and 95% CIs of each study, and used funnel plots to assess publication bias (with study size as a function of effect size)[A: sentence ok as edited?]. We used Egger's linear regression method to test for funnel plot asymmetry (ie, to quantify the bias captured by the funnel plot).[22] Analyses were done with Stata 11 and RevMan 5.

Results

Our initial search yielded 6106 records, of which 4696 remained after removal of duplicates (figure 2). 20 records met our inclusion criteria (table),[23–42] and of these 15 contained the necessary data for inclusion in the quantitative analysis (meta-analysis). Five records were excluded from the quantitative analysis either because Bayesian credible intervals were reported (n=2) or because ORs could not be calculated from the available data (n=3)[A: sentence correct as edited?]. Despite substantial overlap between CIs for both unadjusted and adjusted results, high I^2 values from fixed-effects analysis suggested substantial heterogeneity between studies (unadjusted effect size I^2=68%; adjusted effect size I^2=63%). Therefore random-effects analysis was used.

The meta-analysis was restricted to comparisons between the highest (least poor) and lowest (poorest) socioeconomic groups. Subgroup analysis suggested that low socioeconomic status was associated with increased odds of malaria irrespective of the measure used for socioeconomic status, with the exception of one study in which parents' occupations were used;[31] we therefore judged that to pool all results would be appropriate. In the meta-analyses for both unadjusted and adjusted results, the odds of malaria infection were higher in the poorest children than in the least poor children (figure 3).

Visual assessment of funnel plots (appendix p 7)[A: citation ok here?] showed that the studies were distributed fairly symmetrically about the combined effect size, which suggests little publication bias. However, Egger's test for bias suggested funnel plot asymmetry for the unadjusted results (bias coefficient 1·70, 95% CI −0·97 to 4·37, p=0·191), which suggests that publication bias (delayed publication or location bias), small-study effects, selective outcome reporting, or selective analysis reporting might have been present. A test for funnel plot asymmetry was not possible for the adjusted effects, since only five[A: correct? Changed from fewer than ten to be more accurate] studies were included in the meta-analysis.[A: where in this section should appendix p 5–6 (risk of bias tables) be cited?]

Discussion

[A: I noticed you do not explicitly mention the results of your qualitative analysis (ie, inclusive of the five studies that were excluded from the meta-analysis). It's up to you, but you might want to add a line or two about this to a suitable place in the Discussion, if possible]

Our findings suggest that low socioeconomic status is associated with roughly doubled odds of clinical malaria or parasitaemia in children compared with higher socioeconomic status[A: correct comparator?]. Since our analysis represents a comparison of the very poorest children with the least poor children within highly impoverished communities, the difference in the odds of malaria in the poorest children would probably be even greater if the studies were expanded to include children from wealthier backgrounds. The association between socioeconomic status and malaria is not definitive evidence for the direction of causality, since the poorest households are not only more susceptible to the disease, but are also more vulnerable to its costs, such that the disease itself can induce poverty. For example, a significant positive association between low socioeconomic status and malaria parasitaemia has been reported in Tanzania,[43] with causality in both directions. Findings from Kenya[44] and Nigeria[45] suggest that the costs of malaria treatment (as a proportion of non-food monthly income) and subsequent financial setbacks are greater for poorer than for more wealthy households. Costs also vary geographically; in Kenya[44] and Papua New Guinea,[46] the risk of clinical disease is greater in low-transmission districts, with subsequently greater loss of income.

Wealth is probably protective against malaria, since it renders prophylaxis and treatment more affordable[47–49] and is positively associated with other beneficial factors, including better-educated parents (which improves prophylaxis and treatment for children), increased housing quality (which reduces house entry by malaria-transmitting mosquitoes), and improved nutritional status of children (which could increase their subsequent
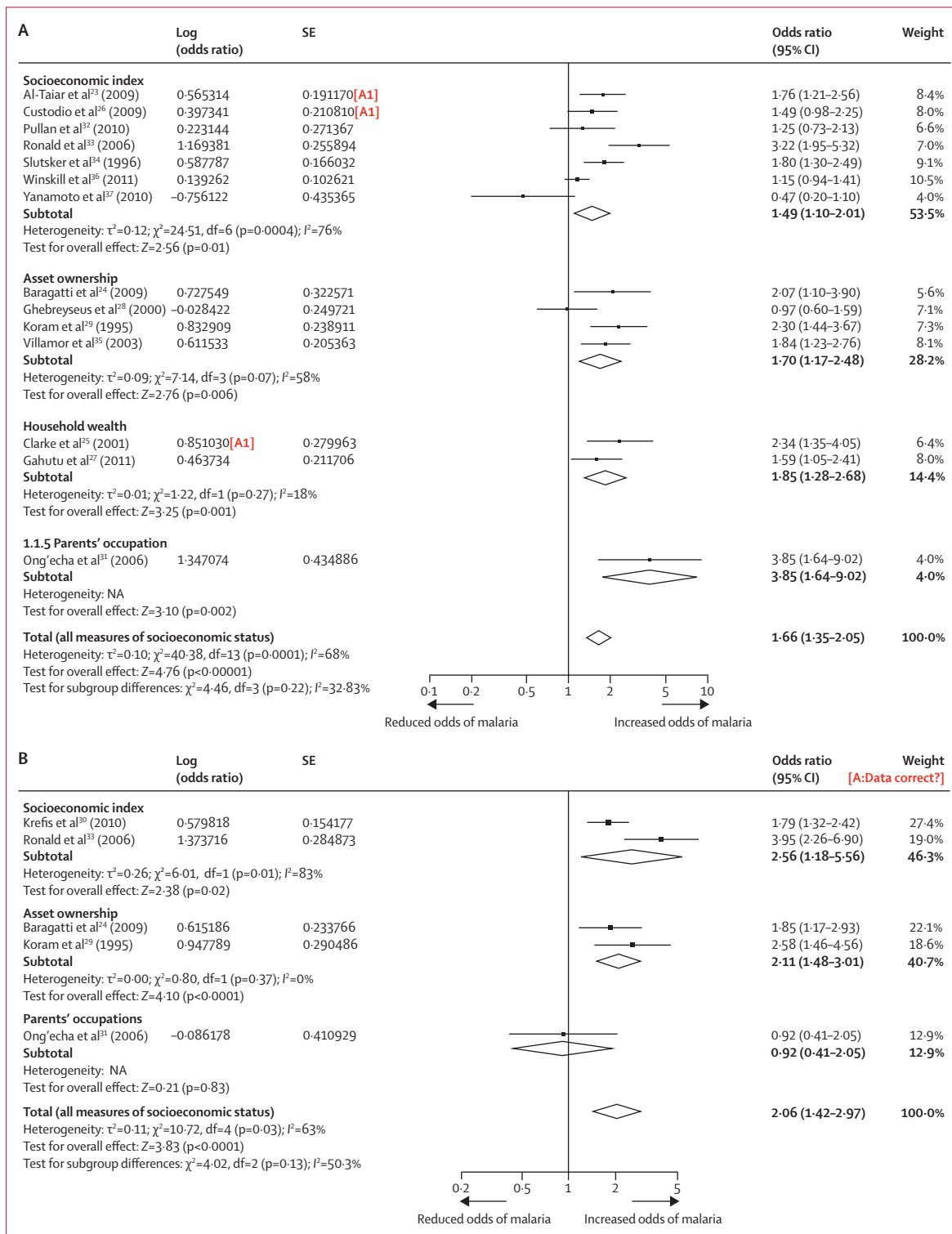
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A

	Log (odds ratio)	SE		Odds ratio (95% CI)	Weight
Socioeconomic index					
Al-Taiar et al[23] (2009)	0·565314	0·191170[A1]		1·76 (1·21–2·56)	8·4%
Custodio et al[26] (2009)	0·397341	0·210810[A1]		1·49 (0·98–2·25)	8·0%
Pullan et al[32] (2010)	0·223144	0·271367		1·25 (0·73–2·13)	6·6%
Ronald et al[33] (2006)	1·169381	0·255894		3·22 (1·95–5·32)	7·0%
Slutsker et al[34] (1996)	0·587787	0·166032		1·80 (1·30–2·49)	9·1%
Winskill et al[36] (2011)	0·139262	0·102621		1·15 (0·94–1·41)	10·5%
Yanamoto et al[37] (2010)	–0·756122	0·435365		0·47 (0·20–1·10)	4·0%
Subtotal				1·49 (1·10–2·01)	53·5%
Heterogeneity: τ²=0·12; χ²=24·51, df=6 (p=0·0004); I²=76%					
Test for overall effect: Z=2·56 (p=0·01)					
Asset ownership					
Baragatti et al[24] (2009)	0·727549	0·322571		2·07 (1·10–3·90)	5·6%
Ghebreyseus et al[28] (2000)	–0·028422	0·249721		0·97 (0·60–1·59)	7·1%
Koram et al[29] (1995)	0·832909	0·238911		2·30 (1·44–3·67)	7·3%
Villamor et al[35] (2003)	0·611533	0·205363		1·84 (1·23–2·76)	8·1%
Subtotal				1·70 (1·17–2·48)	28·2%
Heterogeneity: τ²=0·09; χ²=7·14, df=3 (p=0·07); I²=58%					
Test for overall effect: Z=2·76 (p=0·006)					
Household wealth					
Clarke et al[25] (2001)	0·851030[A1]	0·279963		2·34 (1·35–4·05)	6·4%
Gahutu et al[27] (2011)	0·463734	0·211706		1·59 (1·05–2·41)	8·0%
Subtotal				1·85 (1·28–2·68)	14·4%
Heterogeneity: τ²=0·01; χ²=1·22, df=1 (p=0·27); I²=18%					
Test for overall effect: Z=3·25 (p=0·001)					
1.1.5 Parents' occupation					
Ong'echa et al[31] (2006)	1·347074	0·434886		3·85 (1·64–9·02)	4·0%
Subtotal				3·85 (1·64–9·02)	4·0%
Heterogeneity: NA					
Test for overall effect: Z=3·10 (p=0·002)					
Total (all measures of socioeconomic status)				1·66 (1·35–2·05)	100·0%
Heterogeneity: τ²=0·10; χ²=40·38, df=13 (p=0·0001); I²=68%					
Test for overall effect: Z=4·76 (p<0·00001)					
Test for subgroup differences: χ²=4·46, df=3 (p=0·22); I²=32·83%					

0·1 0·2 0·5 1 2 5 10

← Reduced odds of malaria   Increased odds of malaria →

B

	Log (odds ratio)	SE		Odds ratio (95% CI) [A:Data correct?]	Weight
Socioeconomic index					
Krefis et al[30] (2010)	0·579818	0·154177		1·79 (1·32–2·42)	27·4%
Ronald et al[33] (2006)	1·373716	0·284873		3·95 (2·26–6·90)	19·0%
Subtotal				2·56 (1·18–5·56)	46·3%
Heterogeneity: τ²=0·26; χ²=6·01, df=1 (p=0·01); I²=83%					
Test for overall effect: Z=2·38 (p=0·02)					
Asset ownership					
Baragatti et al[24] (2009)	0·615186	0·233766		1·85 (1·17–2·93)	22·1%
Koram et al[29] (1995)	0·947789	0·290486		2·58 (1·46–4·56)	18·6%
Subtotal				2·11 (1·48–3·01)	40·7%
Heterogeneity: τ²=0·00; χ²=0·80, df=1 (p=0·37); I²=0%					
Test for overall effect: Z=4·10 (p<0·0001)					
Parents' occupations					
Ong'echa et al[31] (2006)	–0·086178	0·410929		0·92 (0·41–2·05)	12·9%
Subtotal				0·92 (0·41–2·05)	12·9%
Heterogeneity: NA					
Test for overall effect: Z=0·21 (p=0·83)					
Total (all measures of socioeconomic status)				2·06 (1·42–2·97)	100·0%
Heterogeneity: τ²=0·11; χ²=10·72, df=4 (p=0·03); I²=63%					
Test for overall effect: Z=3·83 (p<0·0001)					
Test for subgroup differences: χ²=4·02, df=2 (p=0·13); I²=50·3%					

0·2 0·5 1 2 5

← Reduced odds of malaria   Increased odds of malaria →

Figure 3: **Association between low socioeconomic status and clinical malaria or parasitaemia in children aged 0–15 years**
Pooled effects from random-effects meta-analyses for unadjusted (A) and adjusted (B) results are shown [A: ok as worded? What did IV mean next to odds ratio in original figure?]. Studies are divided into subgroups by measure of socioeconomic status used. Error bars show 95% CIs. df=degrees of freedom. [A1: addition of 0 correct? All equivalent values should have same numbers of decimal places]

ability to cope with malaria infection).[50–52] Malaria and poverty therefore constitute a vicious cycle for the poorest households, exacerbating differences in health and wealth.

A major limitation of our meta-analysis is that the measurement of risk factors was done with varying precision in the included studies, and although we did subgroup and random-effects analyses, these are unlikely to have fully accounted for heterogeneity in study design. Another important limitation is the poor quality of the studies included in the meta-analysis, which results from the nature of the study question (since randomisation for socioeconomic status would not be practically or ethically possible). However, the consistency of results across studies and settings suggests that the finding of increased odds of malaria in children of low socioeconomic status is robust. For our systematic review, the main limitation was the language of the search. In particular, not including publications in Spanish probably excluded much data from[A: wording ok?] South America, such that our findings cannot be generalised to that region. Egger's test suggested the presence of some forest plot asymmetry; however, statistical tests for forest plot asymmetry tend to have low power[53] and asymmetry might not be attributable to publication bias—it might also have arisen from poor study quality leading to artificially inflated effects in the smaller studies, selective outcome or analysis reporting, or chance. Incomplete retrieval (four full-text studies could not be retrieved) might also have introduced bias.

On the basis of our findings,[A: addition ok?] we advocate that development programmes should be an essential component of malaria control. Malaria elimination in many high-income countries was achieved without malaria-specific interventions; [A: prevalence?] started to fall in Europe and North America as a by-product of improved living conditions and increased wealth,[54,55] and after Ronald Ross deduced the mode of malaria transmission in 1897[A: please add a reference for this], more specific interventions became possible, including habitat modification (permanent elimination of breeding sites—eg, by installing and maintaining drains), habitat manipulation (temporary creation of unfavourable conditions for the vector—eg, by fluctuating the amount of water in reservoirs), and modifications to human habitation or behaviour to reduce human-vector contact, such as mosquito-proofing of houses.[56] As a result, most of Europe and North America is now characterised by anophelism without malaria, which is testament to the effectiveness of these control efforts, together with a reduced innate receptivity to malaria transmission that stems from advances in nutrition, health care, and development.[57] Similar environmental management strategies, together with larval control, also helped to reduce malaria transmission in many developing countries during the 20th century, including Zanzibar, Indonesia, Malaysia, the Panama Canal, and the Copper Belt of Zambia.[58,59] Thus, as transmission today falls in much of sub-Saharan African and elsewhere, development will contribute to the reduction and elimination of the disease. Several specific development interventions could contribute to malaria control (appendix p 4[A: please check reordered appendix – page citation correct?]), which might be similar to malaria-specific interventions in terms of costs (appendix pp 8–9). An excellent example of how such interventions can work in practice can be seen in Khartoum, Sudan (appendix p 10).

This approach has three major constraints. First, accurate costing of the extent to which specific development interventions contribute to malaria control is difficult[A: sentence ok as reworded?]. Whereas costing[A: do you mean measuring rather than costing? Surely the cost itself is straightforward to establish] the effect of house screening is straightforward, costing[A: as previous query] that of improved education or raised incomes is not. Second, the effectiveness of a development intervention depends on both the nature and intensity of malaria transmission. For example, house screening is probably most effective in areas of low to moderate transmission where vectors feed indoors. Countries that have eliminated malaria since 1900 have largely been temperate, subtropical, or islands,[8] and the high malaria burden in many developing countries is not merely a product of poverty. Rather, the specific ecological requirements of both the malaria parasite and its mosquito vector help to determine the range of the disease.[60] Interventions have to be highly effective and development should not be thought of as a standalone strategy, but as a complement to malaria-specific interventions such as LLINs, indoor residual spraying, and larval source management. Third, economic development gives rise to broader social, environmental, and ecological changes that might [A: in some circumstances?] lead to an increase in the burden of malaria (appendix p 4[A: please check reordered appendix – page citation correct?]), as has been seen in Sri Lanka (appendix p 11)[A: sentence ok as edited? The meaning of "increase as well as decrease" was unclear, and I removed the word global since you are giving a national example]. Nonetheless, these constraints should not be treated as barriers to the use of socioeconomic development as an intervention against malaria (appendix p 4[A: please check reordered appendix – page citation correct?]).

In addition to initiatives such as the Millennium Villages project, which is operating in 12 villages[A: MVP website makes this 14 villages – ok to update text and ref 61? http://www.millenniumvillages.org/the-villages] in ten African countries to examine the effects of socioeconomic development,[61] further research is needed to address some important questions, and to galvanise specialists in both health and development to work more closely together on malaria control. For example, randomised controlled trials should be considered to

assess the effectiveness of socioeconomic interventions (eg, improved education and nutrition) against malaria in different settings. We must also investigate the causal pathways that lead from development to successful malaria control, and vice versa, and develop an understanding of the relation between malaria control, birth rates, and population growth.

That malaria control remains largely the preoccupation of the health sector alone is a failing **[A: of whom/what?]**. The disease severely compromises socioeconomic development, and its control and elimination would improve economic prosperity worldwide. The effectiveness of available drugs and insecticide products**[A: rewording ok (we avoid the word tools)?]** for malaria control will ultimately deteriorate with the emergence of parasites resistant to antimalarials and of vectors resistant to insecticides, and the development and procurement costs of replacements will be high. Donor fatigue is also an ever-present threat to interventions such as LLINs, indoor residual spraying, and intermittent preventive treatment, especially in view of the economic situation since the 2007–08 financial crisis**[A: wording ok?]**.[62] However, several specific development interventions could be introduced to aid both economic development and malaria control. Increased wealth and improved standards of living that stem directly from socioeconomic development could prove fundamental in ensuring that malaria transmission continues to fall in much of Asia, South America, and Africa, as it happened historically in Europe and North America. Socioeconomic development could prove to be a very effective and sustainable intervention against malaria in the long term.

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