Pathways Linking Socioeconomic Position and Malarial Infection and Healthcare-Seeking Behaviour for Suspected Malaria in Sub-Saharan Africa

Dissertation

zur Erlangung des akademischen Grades eines

PhD an der

Medizinischen Fakultät der Universität Hamburg.

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2025

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Datum der mündlichen Prüfung: **27.02.2025**

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List of scientific papers

Thesis is based on the following manuscripts, each referenced within the text using Roman numerals.

I. **Wafula ST**, Habermann T, Franke MA, May J, Puradiredja DI, Lorenz E, Brinkel J. What are the pathways between poverty and malaria in sub-Saharan Africa? A systematic review of mediation studies. *Infect Dis Poverty*. 2023 Jun 8;12(1):58. https://doi.org/10.1186/s40249-023-01110-2. PMID: 37291664; PMCID: PMC10249281.

II. **Wafula ST**, Maiga-Ascofare O, Struck N, Mathanga DP, Cohee LM, May J, Puradiredja DI, Lorenz E. Socioeconomic disparities in *Plasmodium falciparum* infection risk in Southern Malawi: Mediation analyses. *Sci Rep **14**, 27290 (2024). https://doi.org/10.1038/s41598-024-78512-1*

III. **Wafula ST**, Lorenz E, Musoke D, May J, Puradiredja DI, Lamshöft MM. Do wealth, education, and urbanicity promote timely health care seeking and diagnostic testing for febrile children? A meta-analysis of 16 national surveys in sub-Saharan Africa. *BMC Public Health*. 2024 (*Submitted, under Review*)

Further Publications Related to the overall Research Project

IV. Kooko R, **Wafula ST**, Orishaba P. Socioeconomic determinants of malaria prevalence among under five children in Uganda: Evidence from 2018-19 Uganda Malaria Indicator Survey. J Vector Borne Dis. 2023 Jan-Mar;60(1):38-48. doi: 10.4103/0972-9062.353251. PMID: 37026218.

Abstract

Background: Despite advances in malaria prevention and control in sub-Saharan Africa (SSA) over the past two decades, disparities in malaria incidence and healthcare-seeking behaviours for suspected malaria continue to be reported at both national and household levels. This thesis aims to review the evidence on the mediating pathways between socioeconomic position (SEP) and malaria in SSA, to empirically investigate the mediators of this association, and also to assess the socioeconomic disparities in healthcare-seeking practices for the most vulnerable under-five children.

Methods: This PhD research has three main components. **Paper I**, a systematic review was conducted to explore the pathways linking poverty and malaria in SSA. We identified studies that conducted formal mediation analysis, or those that adjusted for SEP and mediators, appraised the mediation methods (if used) and highlighted any strengths and limitations. **Paper II** used secondary data from two large cross-sectional studies conducted in Malawi during the dry and rainy seasons to investigate the underlying socio-structural mechanisms responsible for socioeconomic disparities in *Plasmodium falciparum* infection using a regression-based counterfactual approach to mediation analysis. We presented the Total Natural Direct Effects (TNDEs), Total Natural Indirect Effects (TNIEs) and the proportion mediated (PM). In **Paper III**, a meta-analysis of 16 nationally representative surveys (nine Demographic Health Surveys (DHS) and seven Malaria Indicator Surveys (MIS)) conducted between 2018 and 2023 examined the association between socioeconomic indicators (household SEP, maternal educational attainment, and urban residence) and timely healthcare-seeking and diagnostic testing for children under-five with febrile illnesses. The mediating role of health facility type in the association between SEP and diagnostic testing was also assessed.

Results: The review (**Paper I**) identified food security, housing quality, and previous antimalarial use (prophylaxis) as mediators with education (maternal/household head), long-lasting insecticide treated nets (LLINs), nutrition, and indoor residual spraying as additional potential mediators. The analysis based on the empirical study (**Paper II**) in Malawi identified housing, educational attainment of household head and LLINs as key mediators for the risk of *P. falciparum* infection. The results of the meta-analysis (**Paper**

III) indicated that SEP and maternal educational attainment were responsible for the disparities in timely healthcare-seeking, while gaps in diagnostic testing were primarily driven by differences in SEP. The type of healthcare attended mediated the effect of SEP on diagnostic testing with hospital visits (versus primary care sources) associated with a higher likelihood of receiving diagnostic tests in 14 of 15 surveys.

Conclusion

Findings highlight the need for policymakers to prioritize improving housing conditions, enhancing educational programs on malaria prevention, and ensuring widespread distribution and correct use of LLINs to reduce malaria infection rates. Efforts should also be made to mitigate socioeconomic barriers to healthcare access through providing subsidies for low-SEP families. Additionally, improving the quality of services and accessibility of primary care facilities can ensure timely diagnostic testing and care for children under five with febrile illnesses.

1.0 Synopsis

1.1 Background and context

Malaria remains the most prevalent vector-borne disease globally with nearly half of the world population at risk of contracting the disease. In 2022 alone, it was responsible for an estimated 249 million infections and 608,000 deaths [1]. The vast majority (94%) of cases occur in sub-Saharan Africa (SSA) [1]. Approximately 80% of deaths occur in children under-five making them the most vulnerable population. As of 2023, malaria is endemic in 85 countries and is restricted to tropical and subtropical areas, and altitudes below approximately 1,500 meters dependent on the climate conditions [1] (Fig 1).

In 2021, malaria was the second leading cause of Disability adjusted life years (DALYs) in SSA contributing 39·7 million [16·2 to 77·3] DALYs [2]. The disease also imposes a significant economic burden on families, including out-of-pocket expenditure, lost days at school or work due to an infection, and hinders economic development [3]. The WHO has recommended two malaria vaccines: RTS, S/AS01 and R21/Matrix-M for children under five children. However, their efficacy remains relatively low and uptake has been slow with only three countries currently rolling out the vaccines [1].

Between 2000 and 2015, malaria incidence and deaths decreased by over 30% and 60% respectively in the wake of interventions implemented as part of the Roll-Back Malaria (RBM) programs. Despite this, malaria control has plateaued in the presence of glaring socioeconomic disparities [4]. As part of the response, WHO has developed the Global Technical Strategy for Malaria 2016–2030. This strategy sets ambitious global targets for 2030 with milestones for measuring progress in 2020 and 2025: to reduce malaria mortality rates and malaria case incidence globally by at least 40% by 2020, 75% by 2025, and 90% by 2030, compared to 2015 [5]. Innovative strategies are therefore needed to meet the targets, which have been further derailed by the COVID-19 pandemic [6]. Figure 1. below shows the global distribution of malaria cases in 2022.

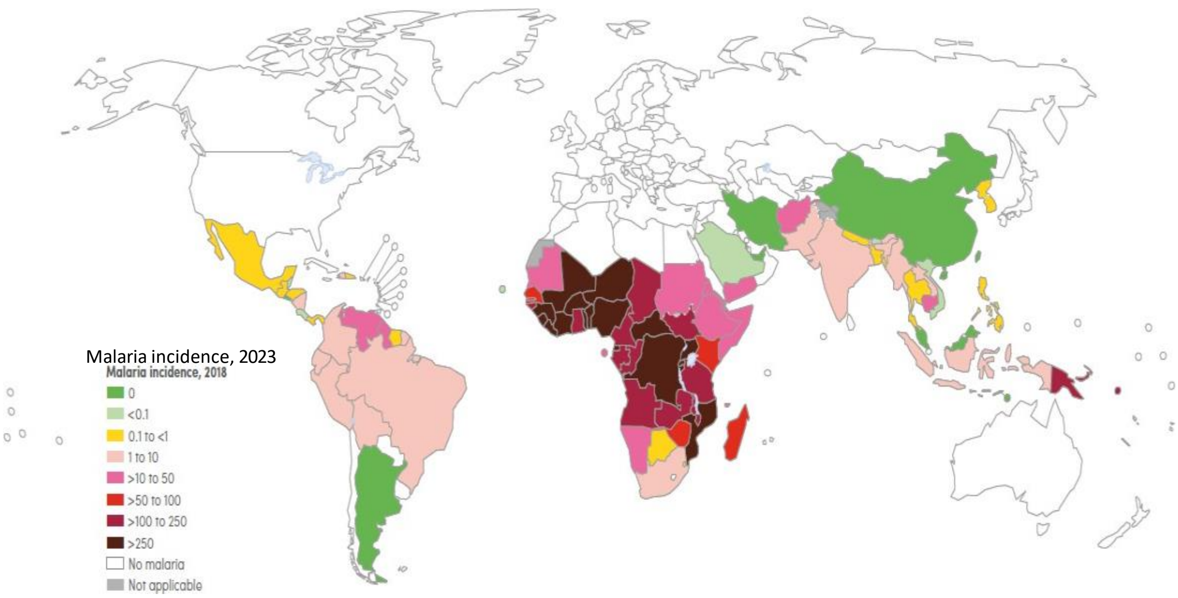

Figure 1: Distribution map of Malaria incidence in 2022[6]

Parasites and the mosquito vectors

Malaria is a disease caused by protozoan blood parasites of the genus *Plasmodium*. Plasmodia are single celled sporozoan parasites that infect red blood cells and are transmitted to vertebrates through the bites of female mosquitoes [7].

Plasmodium falciparum *(P. falciparum),* ***Plasmodium vivax*** *(P. vivax),* ***Plasmodium ovale, Plasmodium malarae****,* and ***Plasmodium knowlesi*** are currently the five species known to infect humans*.* In Africa, *P. falciparum* is the most prevalent in SSA and the one causing most mortality and morbidity. *P. vivax* is a dominant species outside SSA [1]. These parasites are transmitted between humans by mosquitoes of the genus ***Anopheles***.

All Plasmodium species implicated in causing malaria in humans follow a similar life cycle, which starts with an initial development phase in the liver and then proliferating in the host's blood. These species have similar susceptibility to certain antimalarial drugs, such as artemisinin, quinine, and chloroquine and though all they can develop resistance to these treatments [8]. Transmission occurs through the same group of Anopheles mosquitoes. Treatment with drugs that target only the blood stage of the parasite can potentially relapse with *P. vivax* infection [9]. However, primaquine and other 8-aminoquinolines can be effective against relapses. Zoonotic malaria is rare but has been reported especially with *Plasmodium knowlesi* [7]

Diagnosis, clinical features, and complications

Malaria is highly curable especially with timely healthcare-seeking and diagnosis, and appropriate treatment [1]. The presence of *Plasmodium* in the patient's blood, determined by Rapid Diagnostic Tests (RDTs), microscopy, or polymerase chain reaction (PCR) is the primary approach to malaria diagnosis. Biochemistry findings, such as elevated direct or total bilirubin, mild anaemia, thrombocytopenia and elevated aminotransferases can also be suggestive of a positive malaria diagnosis [10]. Malaria can be asymptomatic (no symptoms) or symptomatic. While asymptomatic malaria does not always lead to clinical disease or death, it may lead to anaemia, under-nutrition, low birth weight babies, and can also remain reservoir hosts for future infections [11,12]. For the symptomatic malaria, symptoms appear as a result of toxin production following the destruction of red blood cells by the *Plasmodium* parasites [13]. Symptomatic malaria can be categorised in terms of severity as either uncomplicated or complicated (severe).

The first symptoms of uncomplicated malaria are usually non-specific and appear as flu-like symptoms. The commonest of these include fever and in most cases, up to two days before the onset of fever, and symptoms such as dizziness, anorexia, malaise, dizziness, headache, lumbar and sacroiliac backache, myalgias, nausea, vomiting, chills, and feeling the need to stretch limbs or yawn [14]. Severe malaria complications, on the other hand, predominantly affect individuals without immunity to *falciparum* malaria, and can affect the central nervous system (cerebral malaria), the pulmonary system (respiratory failure), the renal system (acute renal failure), and/or the hematopoietic system (severe anaemia). The rapid progression and potentially fatal nature of severe malaria require that patients are promptly diagnosed and treated patients, with frequent monitoring for early signs of systemic complications. The WHO defines severe malaria as *P. falciparum* asexual parasitaemia, no other apparent cause of symptoms, and having one or more of the symptoms listed in table 1[15]. Cerebral malaria is also a form of severe malaria, which occurs when the disease affects neurological function, causing seizures, unconsciousness, coma, and possibly, death.

Table 1:Clinical and laboratory features of severe malaria [WHO 2021] [15]

Clinical profile:

- Impaired consciousness or unrousable coma
- Prostration, i.e. Generalized weakness so that the patient is unable walk or sit up without assistance
- Failure to feed
- Pulmonary oedema (radiological)
- Deep breathing, respiratory distress (acidotic breathing)
- Circulatory collapse or shock, systolic blood pressure < 70 mmHg in adults and < 50 mmHg in children
- Multiple convulsions (more than two episodes in 24 h)
- Abnormal spontaneous bleeding
- Haemoglobinuria clinical jaundice plus evidence of dysfunction of other vital organs

Laboratory findings:

- Hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- Haemoglobinuria
- Hyperparasitaemia (> 2% or 100,000/μl in low intensity transmission areas or > 5% or 250,000/μl in areas of high stable malaria transmission intensity)
- Hyperlactataemia (lactate > 5 mmol/l)
- Renal impairment (serum creatinine > 265 μmol/l)

Prevention and control strategies

Current malaria control strategies include a combination of vector control approaches and treatment options. These options include case management (diagnosis and treatment), Long-lasting insecticide-treated nets (LLINs), indoor residual spraying (IRS), and intermittent preventive treatment (IPT) among pregnant women. Together, these form the essential package of malaria interventions. While all these strategies are recommended in malaria-endemic countries, in areas of low transmission, all except IPT among pregnant women can be deployed. Additionally, seasonal malaria chemoprevention (SMC) with sulfadoxine-pyrimethamine (SP) and amodiaquine is used in many countries with high transmission peaks, especially for children aged 3-59 months. New evidence has recommended the use of dihydroartemisinin–piperaquine or artesunate–amodiaquine as IPT to reduce malaria and related complications in school-aged children (SAC) and this is already being implemented in Tanzania since 2023 [16]

With the new R21/Matrix-M and RTS,S/AS01 vaccines, many countries in Africa are also starting to scale up malaria vaccines. Strategies are summarised in Table 2

Table 2: *Current Malaria Control Strategies: Vector control, chemoprevention, and diagnosis and treatment* [1,17,18]

Forms of interventions	List of specific strategies
Prevention: Vector control strategies	▪ Insecticide treated mosquito nets (LLINs) ▪ Indoor residual spraying (IRS) ▪ Larval source management and other vector interventions
Pharmaceutical-based intervention / Chemoprevention / Vaccination	▪ Intermittent preventive treatment of malaria in pregnant women (IPTp) ▪ Dihydroartemisinin–piperaquine or artesunate–amodiaquine as IPT school age children. ▪ Seasonal malaria chemoprevention (SMC) for children ▪ Perennial malaria chemoprevention (PMC). SP is delivered during first one to 2 years of life primarily during routine vaccination visits (EPI) platform. ▪ Malaria vaccines: R21/Matrix-M and RTS, S/AS01 to children in endemic areas.
Diagnosis and Treatment	Early case detection and prompt treatment (EDPT) with Artemisinin – based combination therapies

1.1.1. Relationship between socioeconomic status and malaria

Malaria has long been described as a disease of poverty [19,20]. Indeed, as funding to fight malaria were increased from $960 million in 2005 to $2.5 billion in 2014, the global malaria incidence and deaths also declined by 37% and 60% respectively by 2015 [21]. Moreover, over 90% of malaria incidence, mortality and disability-adjusted life years (DALYs) are concentrated in the world's poorest countries. In 2002, Sachs and Malaney also highlighted the inverse association between a country's wealth as measured by its gross domestic product (GDP) and national level malaria incidence [22].

In 2022, there is still an inverse correlation between malaria prevalence, childhood malaria mortality rates, and countries' GDP per capita [1]. Low-income countries, most of which are in SSA, have comparatively higher prevalence rates than high-income countries (Figure 2). Furthermore, countries with a higher proportion of their population living in poverty (less than US$ 1.25 per person per day), had higher malaria mortality rates [23] (Figure 3). Faced with competing financial concerns, the poorest households can find it difficult to prioritize malaria prevention (and treatment) over basic needs, such as food, leaving them particularly vulnerable to malaria.

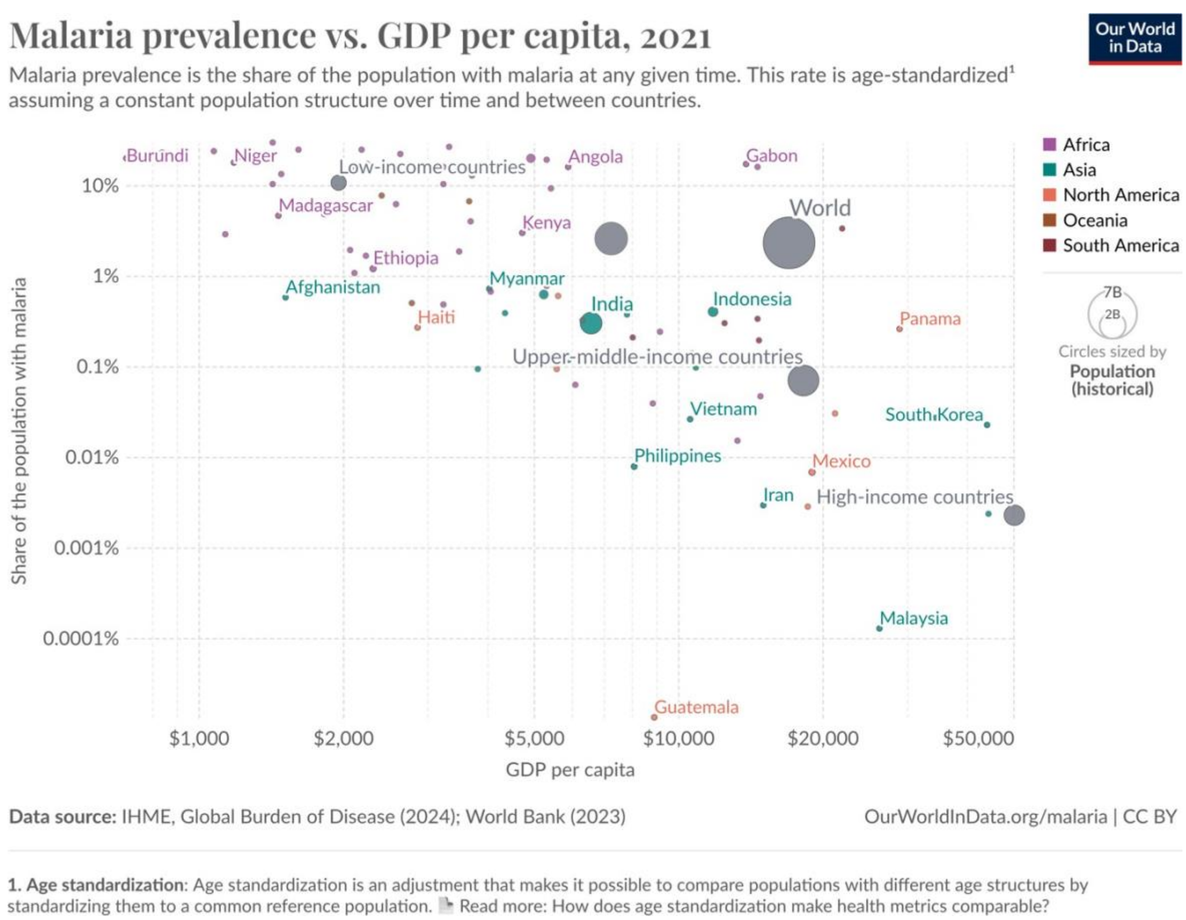

Figure 2: Correlation between GDP per capita and malaria prevalence rates [Our World In Data, 2023] [24]

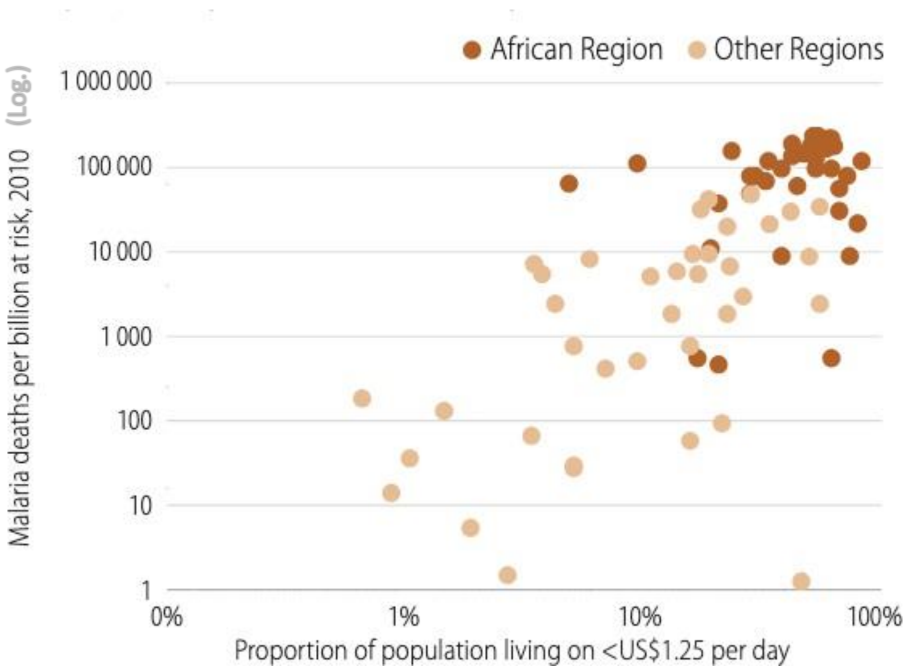

Figure 3: Relationship between proportion of country's population living on <1.25 USD per day and malaria [25]

The above statistics also suggest an association between SEP and malaria at the macro level, but because of their ecological nature, the direction of the association remains unclear due to possible reverse causality and uncontrolled confounding.

At the micro level, the association between socioeconomic status and malaria burden has shown mixed and inconsistent results [26,27]. The inconsistency can be partly explained by differences in the methods used to measure SEP, variations in the population subgroups studied, and the objective measurement of malaria infection [27]. Some studies have measured SEP using asset-based indices constructed using principal component analysis, or multiple correspondence analysis while others have used proxies, such as education, occupation and housing quality. However, most studies indicate that the poorest and most marginalized are the most severely affected by malaria [25]. These communities are at the greatest risk of malaria and have the least access to effective prevention, diagnosis, and treatment services. At the household level, socioeconomic inequalities in malaria incidence have also been highlighted. Members of wealthier households tend to be better protected against malaria than those of households with low SEP [27]. Among those children who are the most vulnerable to malaria mortality, evidence from a recent review indicated that children of households with lowest SEP have two-fold higher odds of having malaria than those of households with highest SEP [28].

Despite recognition of the role of wealth (high SEP) in reducing vulnerability to malaria, most efforts to control malaria focus on biomedical interventions, which are suitable for rapid and large scale-up [29]. However, also in light of increased drug resistance, socio-structural interventions are needed to complement the biomedical interventions [30]. To guide the design and implementation of socio-structural interventions, there is a need to review the evidence regarding the pathways between poverty and malaria in SSA.

1.1.2. Mediated effects of socioeconomic position on malarial infection

SEP remains a key determinant of malarial infection, affecting both exposure to infection and vulnerability to the disease. The effect of SEP on malaria is considered largely indirect [20], potentially mediated by a range of factors including improved housing, education, food security and nutrition, access to health care, and use of LLINs, and indoor residual spraying (IRS). For instance, higher SEP can improve educational attainment, which in turn may promote uptake of health protective measures, such as utilization of LLINs and IRS. Higher SEP can enable families to afford better housing, have improved food security, and have higher health care utilization rates. Moreover, there is a wealth of evidence suggesting that these same factors – education [31], housing [32,33], healthcare-seeking behaviour [34], food security [20], use of LLINs [35,36] and IRS [37] are associated with a reduced risk of malaria. Hence, it is reasonable to hypothesize that these factors mediate (explain) part of the association between SEP and malaria.

As SEP is an important factor but less amenable to direct intervention. Thus, to achieve the desired reduction in malaria risk in the population, identifying more downstream socio-structural factors on the SEP-malaria pathway could represent a more effective approach. Despite the evidence for an association between SEP and malaria, detailed studies elucidating the underlying mechanisms are lacking. At the time, there were no systematic reviews of studies that identified these mechanisms using mediation analysis techniques. A systematic review was therefore needed to identify, summarize, and critically appraise the existing evidence on variables that may mediate the relationship between SEP and malaria in SSA. On the basis of such a review a conceptual framework to guide the design and analysis of future empirical studies could be developed. Such a framework would enable more nuanced analyses of the mediating role of factors on the continuum between poverty and malaria. Identifying these pathways can inform more effective interventions against malaria.

1.1.3. Socioeconomic disparities and healthcare-seeking behaviours for malaria

Since children in endemic areas are at increased risk of severe malarial complications and death [1], any febrile illness is suspected to be malaria and requires timely healthcare-seeking, ideally within 24 hours. However, children in SSA do not consistently receive medical care for fever and those who do so, tend to receive it late [38,39]. Late healthcare-seeking is more common among caretakers of children from low SEP households, which means they are more vulnerable to the complications of malaria [40]. Seeking healthcare promotes appropriate case management, as treatment is more likely to be guided by diagnostic tests as recommended by the WHO before treatment is initiated [41]. However, socioeconomic disparities in diagnostic testing of febrile children persist in SSA, with a significant proportion of children from less educated mothers, from poor or rural households not receiving blood tests.

Since 2015, initiatives promoted by the RBM partnership and global technical strategy initiatives, such as "High Burden, High Impact (HBHI)" and "Zero Malaria Starts with Me" campaigns have seen increased political commitment, funding and health system investments to enhance malaria prevention and access to health care and diagnostics across endemic SSA countries [42,43]. These initiatives prioritize malaria risk stratification and targeted interventions for vulnerable groups and are expected, in part, to reduce the socioeconomic disparities in health care access and diagnostic testing. The hypothesis that SEP, education, and urbanicity influence malaria-related health behaviours (timely healthcare-seeking and diagnostic testing) needs to be re-evaluated. The mediating role of initial healthcare-seeking behaviour and type of health care sought in the association between SEP and diagnostic testing needs further investigation as the direct link may not be as plausible given that most SSA countries have free malaria testing policies [1].

This thesis therefore also reports findings from a meta-analysis of the associations between socioeconomic factors and the timeliness of healthcare-seeking and diagnostic testing in febrile children under five years of age across 16 SSA countries from 2018 to 2023. It also explores the mediating role of health facility type on the association between SEP and diagnostic testing.

1.1.4. Research questions and objectives

The overall aim was to investigate the pathways between socioeconomic position and malaria in sub-Saharan Africa by examining potential underlying mechanisms, as well as socioeconomic disparities in healthcare-seeking behaviours among children under five.

Research Questions:

i. What is the current evidence on the pathways between poverty and malaria in sub-Saharan Africa?

ii. What are the mediators of socioeconomic disparities in *Plasmodium falciparum* infection in Southern Malawi?

iii. Can wealth, education, and urbanicity promote timely healthcare-seeking and diagnostic testing for febrile children?

The specific objectives of this research included:

i. To review the current evidence on the mediators of socioeconomic disparities in malaria in SSA [**Paper I**],

ii. To examine the mediating role of improved housing quality, educational attainment of household head, food security, nutrition, and LLIN use on the association between socioeconomic position and *Plasmodium falciparum* infection in Southern Malawi [**Paper II**].

iii. To conduct a meta-analysis of the associations between socio-economic factors—household SEP, urban residency, and maternal educational attainment—and the timeliness of healthcare-seeking and diagnostic testing for suspected malaria in children under five years of age in 16 SSA countries from 2018 to 2023 [**Paper III**].

1.2. Material and Methods

Between 2021 and 2023, we used quantitative methods in three studies in SSA. Table 3 summarises the study designs and the main analyses conducted.

Table 3*: Summary of the different study designs used in the thesis*

Study	Study design	Analysis	Objective
I	Systematic Review	1. Quantitative synthesis including critical appraisal of the included studies	To provide an overview of the current knowledge / evidence on the mediators of socioeconomic disparities in malaria in sub-Saharan Africa
II	Quantitative (Panel: Two cross-sectional studies)	1. Mediation analysis (counterfactual approach) 2. Sensitivity analysis for unmeasured confounding	To examine the mediating role of improved housing quality, educational attainment of household head, food security, nutrition, and LLIN use on the association between Socioeconomic position and *P. falciparum* infection in Southern Malawi
III	Quantitative: 16 national surveys in SSA	1. Generalised estimating equations (Poisson family); exchangeable correlation structure. 2. Mediation analysis	To conduct a meta-analysis on the associations between socio-economic factors—household SEP, urban residency, and maternal educational attainment—and the timeliness of seeking healthcare and diagnostic testing for suspected malaria in children under five years of age across 16 SSA countries from 2018 to 2023

1.2.1. Review of pathways between SEP and malaria

To understand the state of research on the pathways between poverty and malaria in SSA, we conducted a systematic literature review (the protocol is registered in PROSPERO; Registration ID: CRD42022312359). We searched PubMed and Web of Science (WoS) for English-language studies published from January 1, 2000 and May 31, 2022. A detailed search strategy with a list of search terms was developed.

We included peer-reviewed studies that assessed mediators of SEP (derived from a dimension reduction of owned assets and water and sanitation conditions) and malaria. We also included studies that reported associations between SEP and laboratory-confirmed malaria, including potential mediators as covariates. There were no restrictions on age or gender, as long as the studies were conducted in SSA. We excluded studies that focused on income, education, housing, and occupation as the only SEP dimensions, and those that used self-reported malaria or fever as proxies. Editorials, commentaries, conference abstracts, protocols, case reports, and narrative reviews were also excluded.

Studies were screened at different levels; initial screening of titles and abstracts, followed by full-text review when information in abstracts were insufficient. Relevant data were extracted into a standardized Excel spreadsheet. Existing systematic reviews and reference lists of identified studies were also reviewed. All processes were carried out by two to three independent reviewers, with disagreements resolved by a third review. Duplicates were identified and removed.

Two independent reviewers extracted data from each article using predefined forms to summarise the evidence after full-text screening. We collected information on the first author's name, country of origin, study design, setting, sample size, sampling methods, participant demographics, measures of malaria and SEP, effect estimates (i.e., odds ratios, risk ratios, highest posterior densities), analysis methods (including mediation), covariates, and limitations. For studies with formal mediation analyses, we recorded the percentage of the total effect that was mediated in each pathway.

Quality assessment was performed by two authors using an adapted version of the Effective Public Health Practice Project Tool (EPHPP), which assesses bias in participant selection, study design, confounding, outcome measurement, exposure assessment, and withdrawals and drop-outs (for longitudinal studies) [44]. Each item was rated as weak, moderate, or strong. Studies with no single weak rating were classified as “strong”, those with one weak rating as “moderate”, and those with two or more weak ratings as “weak”. Discrepancies were resolved through discussion.

1.2.2. Mediators of socioeconomic inequalities in Southern Malawi

The analyses presented here are based on data from the International Center of Excellence for Malaria Research (ICEMR) in Malawi, which conducted cross-sectional surveys from 2010 to 2017 [45,46]. The surveys focused on three districts in the southern region : Blantyre City (known for low malaria transmission: prevalence of 5% in the dry season and 9% in the rainy season),Thyolo (moderate malaria transmission - prevalence of 10% in dry and 15% in rainy seasons) and Chikhwawa (high malaria transmission: prevalence of 20% in dry and 32% in rainy seasons) [45]. The main vectors responsible for malaria transmission are include *Anopheles gambiae*, *Anopheles arabiensis,* and *Anopheles funestus* [47]. We used data from two surveys conducted in 2014 during the rainy (April to May) and dry (September to October) seasons. The map of the study area is shown in Fig. 4 below

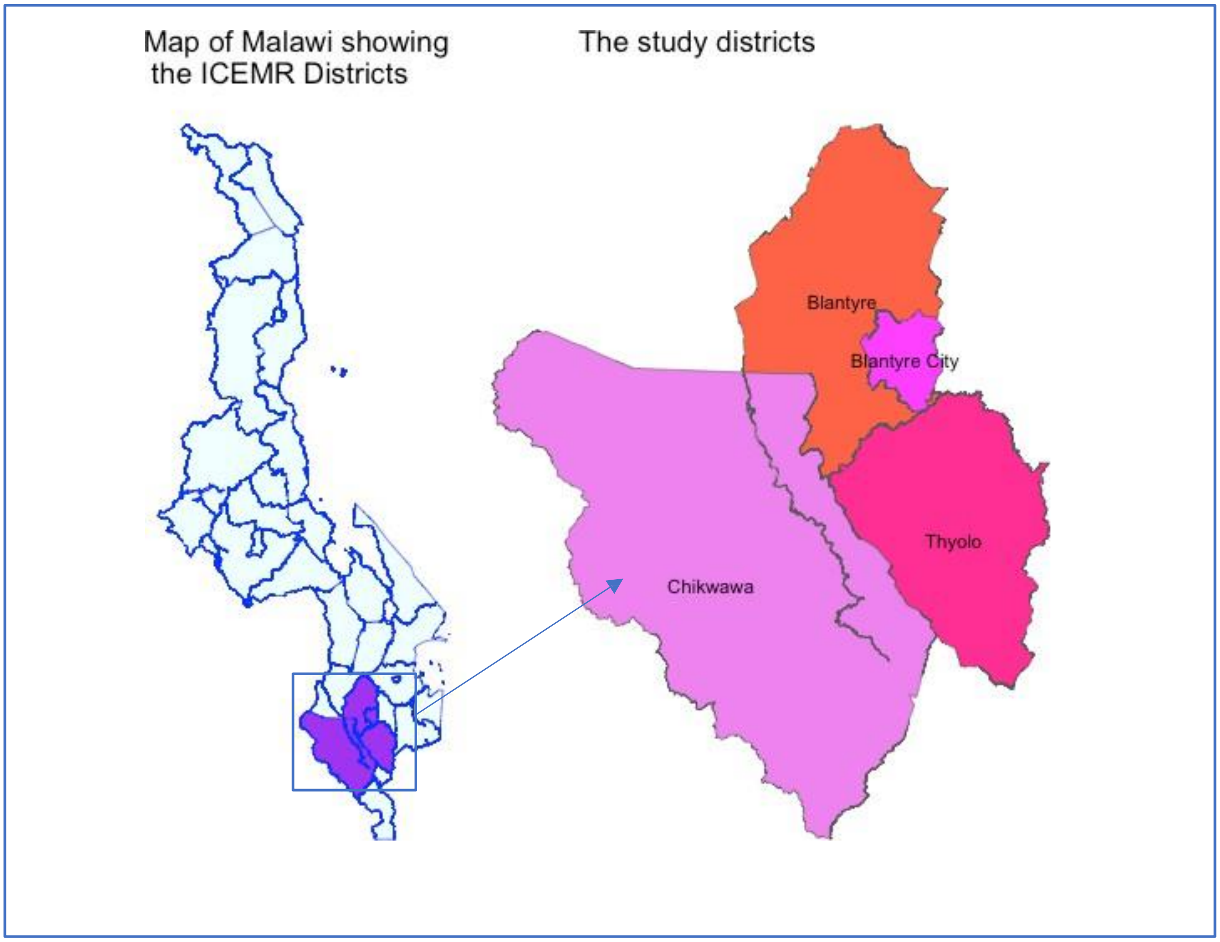

Figure 4: Map of Malawi showing the ICEMR study districts (Created using R software)

A two-stage sampling approach was employed. Initially, 10 enumeration areas (EAs) per district were selected randomly using probability proportionate to size. In Blantyre, only EAs within the city were sampled. In Thyolo, EAs bordering Chikhwawa or those at less than 500m above sea level were excluded. Similarly, in Chikhwawa, EAs bordering Thyolo or EA at greater than 500m above sea level were excluded. If a randomly selected EA met the exclusion criteria, it was replaced by another randomly selected EA. Next, 30 households within each EA were selected using compact segment sampling. Each selected EA was divided into segments of approximately 30 households and one segment was randomly selected. All households within the selected segment were visited, and the household head along with all consenting household members were invited to participate in the study

Data were collected from all members of a selected household in the 30 households in each of the 10 enumeration areas in each district using questionnaires adapted from the Malaria Indicator Survey, covering demographics, asset ownership, LLIN use, housing and food security. Housing characteristics such as wall, floor, roof and eaves were observed and a binary housing quality variable was created where main housing unit was considered high quality if at least three of the four qualities- finished roof material, finished floor material, finished wall material or closed eaves – were present, otherwise it was considered poor quality.

To measure household SEP (main exposure), several socioeconomic indicator variables (durable assets and household characteristics) were considered in a principal component analysis (PCA), a multivariate dimensionality reduction technique [27]. The resulting scores were used to classify households as high (top 20% of scores), middle (scores between 40^{th} and 80^{th} percentile, inclusive) and low (scores ≤ 40^{th} percentile). Mediators included housing quality, educational attainment of the household head, LLIN use, food security, and nutritional status. Fingerpick blood samples were collected for malaria parasite and haemoglobin testing (in children aged 6 months to 15 years). The primary outcome was *P. falciparum* infection measured using PCR technique of DNA material extracted from filter papers [45].

Descriptive statistics were used to summarize baseline characteristics (Rainy season, n = 3,003, dry season, n = 3,253). To examine the association between socioeconomic position (SEP) and *P. falciparum* infection, we utilized two separate regression models for rainy and dry seasons. We employed multivariable mixed-effects modified Poisson regression models, incorporating household as a random intercept to account for intra-household correlations. Adjustments were made for variables including age, sex, household size, and geographical location, with results reported as prevalence ratios (PRs) and 95% confidence intervals (CIs).

We performed causal mediation analyses for the association between SEP and *P. falciparum* infection using the CMAverse package. The mediation analysis examined the influence of factors such as housing quality, usage of long-lasting insecticide-treated nets

(LLINs), food security, educational attainment of household heads, and anemia-free status (only for children aged 6 to 15 years). Regression-based methods, accounting for potential interactions between exposure and mediators, were used to estimate the total effect (TE), total natural indirect effect (TNIE), and total natural direct effect (TNDE). The TNIE reflects the effect of SEP on *P. falciparum* infection mediated by the specified factors, while the TNDE represents the direct effect independent of mediators. The proportion mediated was calculated as TNIE / (TNDE + TNIE) [48,49]. Non-parametric bootstrapping with multiple imputation was used to address missing data for mediators such as LLIN use (0.1%), educational attainment of household heads (0.6%), and covariates including age (0.2%). Counterfactual assumptions included the absence of unmeasured confounding for the treatment-outcome, mediator-outcome, and treatment-mediator relationships. However, being cross sectional design, a temporal sequence between SEP and malaria is complex however since SEP is determined from durable assets, we can assume temporality. Sensitivity analyses assessed the robustness of the estimates to unmeasured confounding, with mediational E-values and 95% CIs reported[50]. Sensitivity analyses using E-value estimation were used to assess the robustness of estimates to unmeasured confounding. The variables for the mediation analysis were guided by a Directed Acyclic Graph (DAG) as shown below (Figure 5).

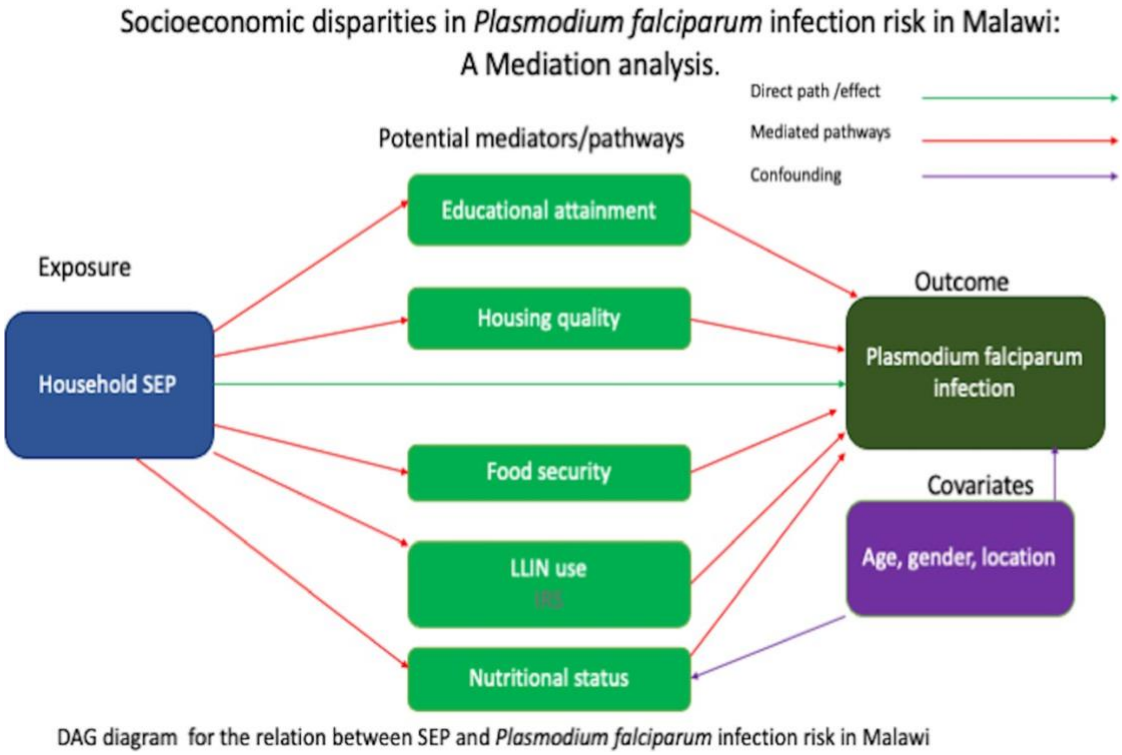

Figure 5: DAG diagram for the association between SEP and the risk of P. falciparum infection

1.2.3. Socioeconomic disparities in healthcare-seeking behaviour

For this study, we used data from 16 nationally representative Demographic and Health Surveys (DHS) and Malaria Indicator Surveys (MIS) conducted in SSA between 2018 and 2023. These surveys included nine DHS (Benin, Burkina Faso, Côte d'Ivoire, The Gambia, Ghana, Kenya, Rwanda, Tanzania, and Zambia) and seven MIS (Cameroon, Guinea, Mali, Mozambique, Niger, Nigeria, and Uganda). The target population was children under five years old, born to women aged 15-49 years. DHS and MIS are standardized cross-sectional surveys conducted in low- and middle-income countries, usually during the dry and rainy seasons, respectively. These surveys use a stratified two-stage cluster sampling design to ensure representativeness. Data from 138,712 children aged 6-59 months were processed and weighted using weights from the women's file. Information collected include detailed information on child, mother, and household characteristics, illnesses among children, and healthcare-seeking behaviour by caretakers/mothers.

The primary outcome was timely healthcare-seeking for suspected malaria among febrile children. Suspected malaria was defined as having a fever within two weeks before the survey. Timely healthcare-seeking was defined as seeking treatment within 24 hours of symptom onset. The secondary outcome was diagnostic testing for malaria which was assessed by asking whether the child had blood drawn for testing during the illness.
Exposure variables were household SEP, maternal educational attainment and urbanicity. The SEP variable generated in the datasets was grouped into three strata: high (5th quintiles), middle (3rd and 4th quintile), and low (1st and 2nd quintiles). Maternal education was categorized as primary or lower and secondary or higher. Urbanicity was defined in terms of residence, i.e., urban or rural. Covariates included children's age and sex, mothers' age, and household size. Mediators assessed were healthcare-seeking behaviour (seeking care vs. home care) and type of health care (hospital vs. primary care).

Descriptive statistics summarized the proportions of children with fever, timely healthcare-seeking, and diagnostic testing. For each survey, we employed generalized estimating equations (GEE) models of the Poisson family with a log link function were used to assess associations between socioeconomic factors and each of the outcomes, adjusting for children's sex and age, and mother`s age. We chose GEE due to instances of multiple participants (children) from the same households, allowing us to account for corelated observations without the strict parametric assumptions. GEE estimates average estimates across all subjects and provides a robust estimation of the within-subject (household) covariance structure. We selected an exchangeable correlation structure as there was no logical ordering for observations within a household and the data was not time series in nature. The PRs and standard errors from 16 surveys were calculated and pooled using random-effects meta-analysis. Subgroup analyses based on survey type (DHS or MIS) and national malaria incidence rates (where appropriate) were conducted. For diagnostic testing, we examined the mediating effects of healthcare-seeking behaviour and type of health care on the association between SEP and testing using a regression-based approach[49]. Natural direct and indirect effects were reported for each survey.

1.3. Results

This chapter presents the main findings derived of studies I, II and III,

1.3.1. Review of pathways between SEP and malaria

Study I summarize the characteristics of the studies included in the review, the key and potential mediators identified, and the strengths and limitations of those studies included. A total of 41 studies (out of 4,924) from 20 SSA countries were included after an extensive literature search using Web of science, PubMed, and through reference checks and recent reviews. The studies varied in design: 30 used a cross-sectional approach, seven were cohort studies, two were case-control studies, and another two were embedded trials. Most studies focused on children as the population of interest, while others included the general population, children and their caretakers, or adult women. SEP was consistently measured using wealth indices derived from household assets, typically categorized into quintiles, quartiles, or tertiles. Some studies treated SEP as a continuous variable or used wealth percentiles, and a few treated it as a dichotomous variable. Malaria outcomes, defined as prevalence or incidence, were assessed using different diagnostic methods: 26 studies used microscopy, 12 used rapid diagnostic tests, two used PCR, and one used histopathology to diagnose placental malaria.

Across studies, there was a consistent finding that higher SEP was associated with a lower risk of malaria. Specifically, 38 studies showed a protective effect of higher SEP against malaria (point estimate), observed in all cross-sectional studies, the majority of cohort/case-control studies, and one cluster randomized trial. The two studies that conducted mediation analyses to explore how SEP might influence malaria risk, examined factors, such as access to healthcare, housing quality, and food security. For instance, one study found that housing quality explained 24.9% of the SEP effect on malaria incidence, while food security explained 18.6%[20]. Another study in Kenya highlighted the protective mediating role of antimalarial use [51]. Several factors were identified as potential mediators based on changes in coefficients between unadjusted and adjusted models and with a protective effect of mediator in adjusted model. These mediators included use of LLINs in 20 out of 26 studies, educational attainment in 12 out of 18 studies, housing quality in 8 out of 11 studies, IRS in 4 of the 5 studies, healthcare-seeking behaviour in 2 out of 3 studies, antimalarial prophylaxis in 2 out of 2 studies, and nutrition in 4 out of 4 studies.

The methodological quality of the reviewed studies was variable: 8 studies were of high quality, 22 of moderate, and 11 of low quality. The main concerns were confounding bias, with some studies controlling for less than 60% of relevant confounders, and selection bias, which was present in 6 studies. The prevalence of cross-sectional designs also limited the ability to make causal inferences about the mediating factors between SEP and malaria.

1.3.2. Mediators of socioeconomic inequalities in southern region of Malawi

In study II, 3,003 individuals (61.3% female) participated in the rainy season survey, and 3,253 (60.9% female) in the dry season survey. The prevalence of *P. falciparum* infection was 19.7% (95% Confidence Interval, CI: 18.4% – 21.3%) in the rainy season, and to 12.9% (95% CI: 11.8% – 14.1%) in the dry season. Fever reported within the past 48 hours were 7.5% in the rainy season and 3.8% in the dry season. Notably, 80.5% of participants had no symptoms during the rainy season, and 83.8% in the dry season. Our findings indicated no significant relationship between household wealth and *P. falciparum* infection risk in either season: rainy season (PR = 0.83, 95% CI = 0.52 – 1.33) and dry season (PR = 0.57, 95% CI = 0.32 – 1.03). Secondary or higher education and better housing were protective factors in both seasons, while the use of LLINs was notably protective in the dry season (PR = 0.52, 95% CI = 0.39 – 0.71).

In the rainy season, single mediator analyses showed that housing quality and secondary or higher education mediated 39.4% and 17.0% of the effect of SEP on *P. falciparum* infection, respectively. When both mediators were considered together, they explained 66.4% of the SEP effect on *P. falciparum* infection. These mediated effects were consistent across different age groups. However, the indirect effects through individual mediators, such as housing and education were less robust to unmeasured confounding, as indicated by lower E-values. Higher E-values suggest a stronger association that is less susceptible to confounding.

During the dry season, housing quality, secondary education or higher of the household head, and LLIN use mediated 15.6%, 11.3%, and 3.7% of the SEP effect on *P. falciparum* infection, respectively. Combined, these mediators explained 33.4% of the SEP effect. The total natural indirect effects (TNIEs) from individual mediator analyses were again less robust to unmeasured confounding, compared to those from multiple mediator analyses. Findings from subgroup analyses (based on age) are available as supplementary file [refer to file **Supplementary** File 5].

1.3.3. Socioeconomic disparities in healthcare-seeking behaviour

Healthcare-seeking behaviour and diagnostic blood testing

In study III, 29,708 of 138,712 children had febrile symptoms in the two weeks prior to the surveys, and 66.3% sought medical advice or treatment. Uganda had the highest rate of healthcare-seeking at 86.8%, while Benin had the lowest at 53.1%. Of those who sought care, 58.4% did so within 24 hours of symptom onset, in line with WHO guidelines. Timely healthcare-seeking was highest in The Gambia (77.7%) and lowest in Mali (40.7%).

The proportion of children with fever who were tested for malaria varied widely. Burkina Faso had the highest testing rate at 65.2%, while Benin had the lowest at 17.8%. On average, 38.2% of children were tested in the surveyed countries

Socioeconomic indicators and timely healthcare-seeking

Findings indicated that children from middle (PR = 1.09, 95% CI 1.04 – 1.14) and higher socioeconomic strata (PR = 1.18, 95%CI 1.11 – 1.26) were more likely to access timely health care compared to children from households with lower SEP. This trend was observed in both the DHS and MIS surveys with a marginally stronger effect noted in MIS. In countries such as Burkina Faso, Mali, and Nigeria and in countries with a malaria incidence of ≥ 300 cases per 1,000 population, Secondary school education or higher (of the mother) was positively associated with timely healthcare-seeking (PR = 1.11, 95%CI 1.01 – 1.23). However, the pooled estimate from all countries showed no significant association with timely healthcare-seeking (OR = 1.04, 95%CI = 1.00 – 1.10). Living in an urban area was not associated with timely healthcare-seeking (PR = 1.01, 95%CI 0.96 – 1.06).

Socioeconomic indicators and diagnostic testing

Children from households with a higher SEP were 15% more likely to be tested for malaria than children from households with a lower SEP (PR = 1.15, 95%CI 1.03 – 1.28). This disparity was more pronounced in DHS surveys than in MIS surveys. Maternal education beyond primary level and urban residency were not significantly associated with the likelihood of diagnostic testing.

Mediation analysis

Our analysis revealed that SEP plays a significant role in influencing healthcare-seeking which in turn increases the likelihood of receiving diagnostic tests. This indirect effect was observed in 81.3% (13/16) of the surveys, with exceptions in Tanzania, Ghana, and the Gambia.

The choice between hospital and primary care influenced diagnostic testing. SEP impacted this choice, with higher SEP often leading to hospital care, which was associated with higher odds of diagnostic testing (13/15), except in Uganda (OR = 0.89, 95%CI 0.84 – 0.91) and Ghana (OR = 0.92, 95%CI 0.84 – 0.94).

1.4. Discussion

1.4.1. Review of pathways between SEP and malaria

Our review indicates that mediators of the association between household SEP and Malaria are still under-researched. Only two studies formally assessed mediators of SEP and malaria pathways (housing quality, food security, antimalarial use). Results from one of these studies indicated that housing quality and food security may mediate socioeconomic differences in malaria risk. Specifically, housing quality and food insecurity mediated 24.9% and 18.6% of the effect of SEP on malaria incidence, respectively [20].

The study also suggested that treatment-seeking behaviour may play a mediating role; however, the authors did not perform a robust mediation analysis due to insufficient sample size. The study analyses were informed by a conceptual framework that did not operationalize pathways, such as access to healthcare, use of ITNs, or education in its mediation analyses. The proportion of the socioeconomic differences in malaria mediated by housing and food security was small (less than 30%), suggesting that other potential mediators could explain some of the effect of SEP. Some assumptions for mediation were not always met (including potential reverse causality and identifiability), and many analyses did not consider interactions or adjust for mediator outcome confounding, which raises concerns about the validity of the reported mediation effects. Future studies need to apply more robust analyses to longitudinal data where many assumptions may hold. Nevertheless, they showed that incremental improvements in housing quality and interventions, such as irrigation and agriculture could promote food security, and thereby protect against malaria. In another study [51], prophylactic antimalarial treatment was also found to mediate the association between SEP and malaria infection. However, this study did not provide information on the proportion of the effect that was mediated, nor did it test the assumptions of identifiability, so the results must be interpreted with caution [51].

Evidence from 39 other studies suggested that the use of LLINs, higher education, better nutrition, housing quality, IRS, and the use of repellents could protect against malarial infection. Again, these studies did not conduct formal mediation analyses, but included potential mediators as covariates with SEP. While it is generally not recommended to control for mediating variables in the causal relationships, as conditioning on mediators leads to underestimation of the total effect of exposure [52], the attenuation of the coefficients of SEP in a multivariable model suggests that they may be mediators. The potential mediators included higher education [34,53-58], use of IRS [57,59-61], better housing [32,56,62-67] and use of LLINs. In light of this evidence, there is a need to assess the mediating roles in empirical studies in different settings and their relative contributions to the association between SEP and malaria. This information can inform policy makers in the design and implementation of more appropriate targeted socio-structural interventions against malaria.

1.4.2. Mediators of socioeconomic inequalities in the Southern region of Malawi

In investigating the mediated (indirect) effects of SEP on *P. falciparum infection, the* potential mediating roles of housing quality, food security, LLIN use, educational attainment of household heads, and nutritional status (haemoglobin) were evaluated in both dry and rainy seasons.

We found that housing quality partially mediated the association between household SEP and *P. falciparum infection* in both rainy and dry seasons with a more pronounced effect in the rainy season. Higher SEP was strongly associated with improved housing, and improved housing in turn was protective against *P. falciparum infection*, meeting Baron and Kennys' main criteria for a potential mediator [68]. Improved housing may prevent the entry of mosquito vectors and thereby reduce the mosquito biting rates, especially at night/evening, which in turn reduces the risk of *P. falciparum* infection [33]. Since most transmission occurs at night [69], the dwelling can be a risky place and needs to be well constructed and screened to prevent mosquito entry. While the direct effect of SEP was more robust to unmeasured confounding, the indirect/mediated effect through housing was less robust, which suggests that a confounding variable with risk ratio (RR) of 2 would effectively explain away the observed mediated effect to cross the null. However, this finding is still important to guide the design of houses, such as closing eaves or closing all possible entry points for mosquitoes indoors.

We also found that reported LLIN use explained 3.7% of the effect of SEP on *P. falciparum* infection in the dry season. This underscores the protective effectiveness of LLINs against *P. falciparum* infection and the influence of SEP on their use as previously highlighted [35,36,70]. In Malawi, universal bed net coverage has not yet been achieved, because insufficient quantities of LLINs are distributed free of charge [71]. The mediating role of LLIN use was not replicated in the rainy season. The absence of a mediated effect during the rainy season could be attributed to increased exposure to mosquitoes during outdoor activities and a higher indoor mosquito population, which means that people are more likely to be bitten before they use the LLINs while sleeping in the evenings. This negates some of the protection provided by LLINs and requires the use of additional control measures. The low E-values associated with the mediated effects observed in the dry season suggest vulnerability to unmeasured confounding, so the findings should be interpreted with caution. Nonetheless, even a modest mediated effect suggests that improving universal LLIN coverage could help reduce the risk of *P. falciparum* infection, highlighting the critical need to increase distribution efforts.

Education has been shown to have a positive impact on a number of health-related outcomes. In this study, we also found that having a household head with secondary or higher education partially explained the association between SEP and risk of *P. falciparum infection* among household members. This was also confirmed in subgroup analyses based on season and age – except for adults in the dry season. We hypothesize that a higher SEP enables a high educational attainment, which may then ensure better knowledge and use of preventive measures such as LLINs, clearing breeding grounds, proactive acquisition of insect sprays, which consequently reduces exposure to mosquito vectors and hence the risk of *P. falciparum* infection [72]. Moreover, higher education can also come with greater financial power to procure some of these preventive measures but may also facilitate earlier symptom recognition, and timely treatment seeking [73]. This shows that improving educational attainment is an important socio-structural intervention that should be promoted as part of long-term malaria eradication efforts.

While this study found a protective effect of SEP mediated by housing modifications and LLINs, it is important to note that vector behaviour has changed in response to widespread LLIN use in recent years with more biting now occurring in the evening and morning, which may render housing less effective [74]. This will require further measures to control vector entry into homes or nets. We have also demonstrated that using a combination of mediators — improved housing, education, LLIN use — has a synergistic effect on reducing the risk of *P. falciparum* infection. Targeting multiple mediators appears to be more effective than single-mediator strategies and findings were more robust to unmeasured confounding. Notably, the impact of these mediators is magnified during the rainy season, a period of heightened malaria transmission, underscoring their critical importance. In the rainy season, the combined effect of these mediators is particularly pronounced in adults but also in children under 5 who represent the age group with the highest malaria-related mortality. The results underscore the need for integrated malaria control measures that address multiple risk factors simultaneously.

This is one of the first studies to consider multiple socio-structural mediators of the association between SEP and *P. falciparum* infection, both individually and jointly, adding to the body of knowledge on the relationship between wealth/poverty and *P. falciparum* infection. Our study contributes to the malaria control efforts by providing more comprehensive results from a counterfactual perspective. Limitations of this study include the inability to make causal claims due to the cross-sectional design and a challenge of temporality, however, most of the exposures and mediators are structural and long-term, so we can be reasonably sure that they preceded the onset of malaria. Another limitation is that the nature of the design violates the stringent identifiability assumptions required for causal interpretation, but sensitivity analysis for unmeasured confounding was conducted to guide the causal interpretation. Potential measurement error in some of the mediators, such as food security and LLIN use (self-reporting bias) which may introduce bias either direction (towards or away from the null) and affect the robustness of the findings, however, these results still provide an important source of hypotheses for future longitudinal studies.

1.4.3. Socioeconomic disparities in healthcare-seeking behaviour

In study III, we assessed the association between socioeconomic barriers to care — household SEP, maternal education and urbanicity, and timely healthcare-seeking and diagnostic testing. We further assessed if progress has been made in the context of recent large-scale initiatives to reduce malaria mortality and morbidity.

In SSA, where *P. falciparum* malaria is endemic, timely healthcare-seeking and diagnostic testing for paediatric fever are critical for effective management. Our findings reinforce the important role of socioeconomic disparities in shaping health care behaviours. Belonging to a middle or higher SEP stratum was associated with timely healthcare-seeking, which is corroborated with previous studies [40,70,75] that also highlighted SEP disparities in timely healthcare-seeking. However, we observe smaller disparities than previously reported, which we hypothesize may be influenced by recent investments in malaria control initiatives. Although primary health care services are free of charge in most countries, barriers such as transport costs, diagnostic and medication shortages, and long waiting times persist and disproportionately affect caregivers from lower SEP households. These barriers not only delay treatment but also exacerbate health inequities, as highlighted in previous studies [76,77].

The effect of maternal education on timely healthcare-seeking was not strong overall, except in Burkina Faso, Mali, and Nigeria. This was particularly the case in countries with malaria incidence of ≥300 cases per 1,000. Secondary or higher education enables more proactive seeking of timely healthcare, reflecting a context-dependent effect of education. Previous studies have shown that in high-transmission settings, a higher proportion of fevers can be attributed to malaria with more educated mothers perceiving these risks and seeking healthcare in a shorter time [78,79]. These findings are consistent with other studies [80,81] showing a positive association between maternal/caregiver education attainment and timely healthcare-seeking in high-endemic settings.

We find that higher SEP was also associated with an increased likelihood of febrile children undergoing diagnostic testing, consistent with other studies in SSA [75,82]. Crucially, the study identified the type of health care sought as an important mediator of the association between SEP and diagnostic testing. Caregivers with higher SEP were more likely to seek care at better-equipped health care facilities, such as hospitals, which tend to offer more comprehensive diagnostic services. While most countries, with the exception of Nigeria and Cameroon, have free-of-charge diagnostic testing policies, regular shortages of diagnostic equipment at primary care facilities can hinder diagnostic testing [1]. This is of particular concern because families from lower socio-economic strata in more remote areas often seek care at such facilities [83]. This underscores the importance of addressing structural barriers to health care access, as highlighted in the literature [84].

Our findings should be viewed in the context of major malaria control programs such as the RBM initiative and Integrated Community Case Management (iCCM). The RBM partnership has significantly increased the use of LLINs, IRS, and RDTs, while iCCM has trained community health workers (CHWs) to provide care in remote areas [85]. Despite these efforts, our study reveals continuing challenges, particularly socioeconomic disparities in healthcare utilization. Potential interventions could focus on ensuring that diagnostics are available in all primary care and private facilities, or subsidizing them, to reduce opportunity and direct costs. This would make diagnostic testing accessible to all children. Our findings emphasize the need for interventions to promote healthcare-seeking behaviours, especially among those in need, and to improve access to malaria diagnostic testing at primary healthcare levels.

A major strength of this study is its comprehensive and rigorous meta-analysis, using individual-level data from large, nationally representative surveys. Unlike many secondary analyses, our study is robust because of consistent adjustments for the same covariates across different models using individual survey data. The aggregation of multiple datasets results in a large sample size, which improves the precision of the estimates. The use of recent data ensures timely relevance, particularly for evaluations of post-2015 interventions. However, the study has also some limitations. The absence of certain contextual and behavioural factors in the DHS/MIS surveys limits our ability to explain unexpected findings, such as the indirect effect of SEP on diagnostic testing (through facility type) in Guinea and Uganda. This highlights the need for additional data collection methods. Additionally, classifying shops and markets—typically lacking diagnostic testing—as primary care may slightly overestimate the mediating role of hospital care. Nonetheless, this overestimation is minimal, as these facilities account for less than 5% of patient visits.

2.0. Publications

2.1. What are the pathways between poverty and malaria in sub-Saharan Africa? A systematic review of mediation studies

Wafula *et al. Infectious Diseases of Poverty (2023) 12:58*
https://doi.org/10.1186/s40249-023-01110-2

Infectious Diseases of Poverty

SCOPING REVIEW

Open Access

What are the pathways between poverty and malaria in sub-Saharan Africa? A systematic review of mediation studies

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Abstract

Background Malaria remains a major burden in sub-Saharan Africa (SSA). While an association between poverty and malaria has been demonstrated, a clearer understanding of explicit mechanisms through which socioeconomic position (SEP) influences malaria risk is needed to guide the design of more comprehensive interventions for malaria risk mitigation. This systematic review provides an overview of the current evidence on the mediators of socioeconomic disparities in malaria in SSA.

Methods We searched PubMed and Web of Science for randomised controlled trials, cohort, case-control and cross-sectional studies published in English between January 1, 2000 to May 31, 2022. Further studies were identified following reviews of reference lists of the studies included. We included studies that either (1) conducted a formal mediation analysis of risk factors on the causal pathway between SEP and malaria infections or (2) adjusted for these potential mediators as confounders on the association between SEP and malaria using standard regression models. At least two independent reviewers appraised the studies, conducted data extraction, and assessed risk of bias. A systematic overview is presented for the included studies.

Results We identified 41 articles from 20 countries in SSA for inclusion in the final review. Of these, 30 studies used cross-sectional design, and 26 found socioeconomic inequalities in malaria risk. Three formal mediation analyses showed limited evidence of mediation of food security, housing quality, and previous antimalarial use. Housing, education, insecticide-treated nets, and nutrition were highlighted in the remaining studies as being protective against malaria independent of SEP, suggesting potential for mediation. However, methodological limitations included the use of cross-sectional data, insufficient confounder adjustment, heterogeneity in measuring both SEP and malaria, and generally low or moderate-quality studies. No studies considered exposure mediator interactions or considered identifiability assumptions.

Conclusions Few studies have conducted formal mediation analyses to elucidate pathways between SEP and malaria. Findings indicate that food security and housing could be more feasible (structural) intervention targets. Further research using well-designed longitudinal studies and improved analysis would illuminate the current sparse evidence into the pathways between SEP and malaria and adduce evidence for more potential targets for effective intervention.

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Keywords Malaria, Mediation, Socioeconomic disparity, Sub-Saharan Africa

Background

Malaria is considered a disease of poverty [1]. Approximately 90% of all malaria-related morbidity and mortality occur in the world's poorest regions, such as sub-Saharan Africa (SSA) [2]. Evidence of socioeconomic inequali- ties in the malaria burden has been consistently docu- mented [1, 3]. Recent systematic reviews show that greater household wealth is associated with reductions in malaria [4–6]. For instance, evidence indicates that the risk of malaria is halved in children from the least poor households compared with those from the poorest households [4, 7]. Previous studies have used different proxies such as education, urbanicity, occupation, housing, and income to define socioeconomic position (SEP) [4, 6]. These proxies are either difficult to measure, have untestable assumptions about the link between indicators and poverty or sometimes comparisons across contexts/settings are not always valid. While household consumption is a better measure than income because it is less affected by inflation, measuring it is time-consuming and subject to bias [8]. A recently validated methodological approach that employs wealth indices derived from household assets, housing and living conditions is rarely used [9].

However, the impact of improved SEP on malaria may be largely indirect [1]. Indeed, studies show that socioeconomic disparities in malaria may be partly explained by factors on the causal pathway, such as improved housing, education, nutrition, food security, and use of insecticide-treated nets (ITN) [1, 10, 11]. If a causal rela- tionship exists between SEP and malaria, then mediating pathways between SEP and malaria may be viable targets for interventions to reduce malaria incidence. Mediation analysis helps to understand whether and to what extent a third (intermediate) variable explains an exposure's effect by partitioning the total effect of exposure into direct and indirect effects [12, 13]. The mediation analysis is depicted in Fig. 1 where a = coefficient of the path from exposure (E) to mediator (M), b = coefficient of the path from M to outcome (O) and c′ = coefficient of the path from E to O. The path c′ is the direct effect of E on O while the indirect effect of E is through a and b [14].

The difference method and the product of coefficients method are two conventional approaches biomedical researchers have used to conduct mediation analysis, but they both have drawbacks. The recent developments in the causal inference literature have made it possible to conduct mediation analysis with exposure-mediator interactions, multiple mediators, and counterfactual outcome perspectives [14]. In light of these methodological developments, reviewing the current evidence of the mediators between SEP and malaria provides helpful information to guide future analyses.

Although extant evidence supports the association between SEP and malaria, there is a lack of detailed studies to elucidate the underlying mechanisms behind this association and assess the evidence in light of the recent developments in mediation analysis. To our knowledge, there is no systematic review of studies that apply mediation analyses to investigate the underlying mechanisms between SEP and malaria. There is also a lack of syn- thesis of studies in which potential mediators have been adjusted for in the analyses. Therefore, this systematic review aims to comprehensively identify, summarize and

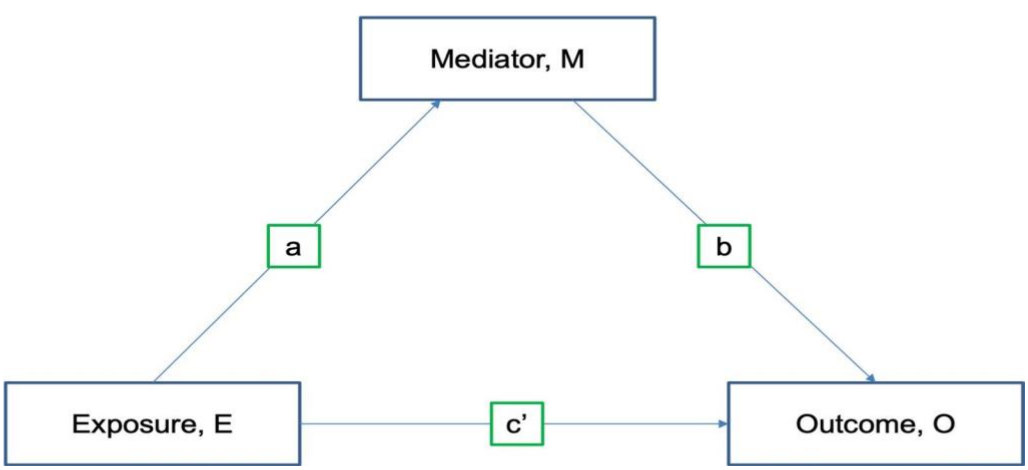

Fig. 1 Relationship between exposure E, mediator M and outcome O

critically appraise the existing evidence regarding variables that potentially mediate the relationship between SEP and malaria in SSA. Highlights of the review have been provided (Additional file 1: Table S1).

Methods

Search strategy and selection process

This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (PRISMA-P) 2020 statement [15] and registered in PROSPERO in March 2022 (Registration ID: CRD42022312359). We searched PubMed and Web of Science (WoS) for studies published in the English language for the period between January 1, 2000 and June 30, 2020 and updated in May 2022. A search strategy was developed to identify studies reporting on mediators of socioeconomic inequalities in malaria in SSA. A list of search terms and a detailed search strategy are provided (Additional file 1: Table S2).

Inclusion and exclusion criteria

We included all studies that quantitatively assessed mediators of SEP (derived from asset ownership and water and sanitation status) and malaria. We also included studies that reported associations between SEP and laboratory-confirmed malaria and simultaneously included potential mediators as covariates. The study population was not restricted to any age or gender, provided the studies were conducted in SSA [16]. We considered peer-reviewed articles published between January 1, 2000, and May 31, 2022, as eligible for inclusion. Studies that only considered one dimension of SEP, such as income, education, housing, occupation, and those using self-reported malaria or fever as a proxy for malaria, were excluded from this review. We excluded editorials, commentaries, conference abstracts, protocols, case reports and narrative reviews.

Identification of studies and data extraction

The screening was done at different stages. First, the authors (MAF and THH) screened all titles and abstracts of retrieved articles. We evaluated full texts when the abstract was deemed insufficient to draw conclusions. Full texts were then screened by three independent reviewers (STW, MAF, and THH) who extracted all relevant information into a standardized Excel spreadsheet. We also searched existing systematic reviews and reference lists of identified studies in addition to the electronic search. For excluded studies, reasons for exclusion were recorded. In case of discordance, the question of the inclusion of articles was resolved by a discussion with a reviewer panel (EL, JB, DIP). The comprehensive search results were merged, and duplicates were verified and removed.

Two independent reviewers (STW and THH) extracted relevant data from each paper using prepared data extraction forms to summarise evidence after the full text screening. We collected information on the first author's name, country of origin, study designs, study settings, sample size and participant characteristics (age, gender, domain), sampling methods, indicators of malaria and SEP, effect estimates (i.e., odds ratios, risk ratios, highest posterior densities), analysis methods (including mediation), covariates, and limitations. For studies that performed formal mediation analyses, we captured data on the percentage of the total effect that was mediated in each pathway.

Study quality assessment

Two authors (SWT and MAF) undertook quality assessment using an adapted version of the Effective Public Health Practice Project Tool (EPHPP) [17] (Additional file 1: Table S3). We evaluated the quality of individual studies based on participant selection, study design, control of confounding, measurement of outcome, assessment of the exposures, and withdrawals and dropouts (for longitudinal studies). We rated each item as weak, moderate, or strong according to the quality assessment criteria and determined an overall global rating for the included studies. We categorized studies into strong, moderate, and weak based on the criteria. Studies with no weak component ratings were assigned as "strong". Those with one weak component ratings were assigned "moderate", while those two or more weak component ratings received "weak" quality ratings. We resolved any discrepancies through discussion. Details of the ratings are available (Additional file 1: Table S4).

Data synthesis strategy

Due to significant heterogeneity in the studies in terms of study designs, study populations, and settings, a comprehensive narrative synthesis was performed to answer the review's objective. Study findings have been presented in tabular form, highlighting country, year of study, study population, context, mediators considered, and outcome measurement, among others.

Patient and public involvement

No patients were involved in the conceptualisation or conduct of this study due to the nature of the study as a systematic review.

Results

Search results and eligible studies

A total of 4914 articles were obtained after searching literature from the two databases. An extra 10 articles were identified by reviewing references of included studies [18–23] and relevant recent systematic reviews [24–27]. Of the 4924 articles, 537 were found to be duplicates. After screening the titles and abstracts, 217 were retained and determined as eligible for full text review resulting into 176 articles being excluded and leaving 41 articles. A flow chart including details of the article screening pro- cess is shown (Fig. 2).

Characteristics of included studies

Forty-one (41) studies were conducted in 20 countries in SSA. The review had eight studies conducted in Tanzania [21, 23, 28–33], and Malawi [23, 34–40] and seven studies from Uganda [1, 22, 23, 25, 41–43], four in Ethiopia [18, 19, 44, 45], three in Kenya [46–48], two in Ghana [27, 49], the Gambia [27, 49], and Burkina Faso [49, 50], Democratic Republic of Congo (DRC) [51, 52], Nigeria [23, 53], Mali [49, 54], Mozambique [55, 56], while Cameroon [57], Equatorial Guinea [24], Angola [23], Liberia [23], Rwanda [23], Senegal [23], Madagascar [23] and South Africa [20] all had one study.

Of the 41 studies, 30 used a cross-sectional design [19, 23–25, 27, 28, 30–40, 42, 45–47, 49–53, 55–58], seven used a cohort design [1, 18, 22, 26, 41, 43, 54], two were case–control studies [20, 48], and two investigations were embedded trials [29, 44]. All studies used objective diagnostic malaria tests, and most studies (26) had children as their population, eight had the general population, six considered both children and their caretakers, and two

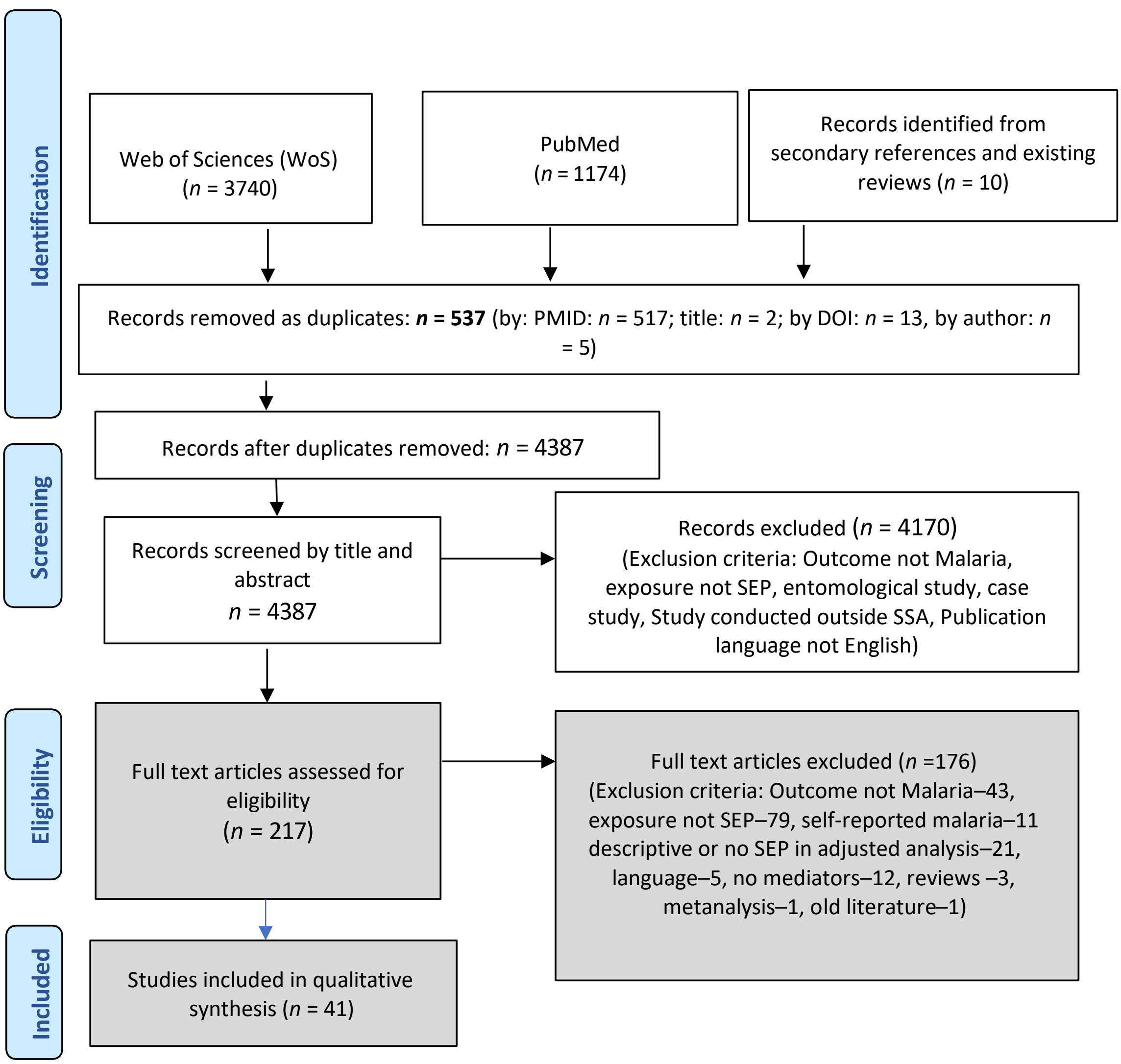

Fig. 2 PRISMA flow diagram for study screening and selection process. *DOI* digital object identifier, *PMID* PubMed identifier, *SEP* socioeconomic position, *WOS* web of science

considered adult women. The characteristics of included studies are included in Table 2.

Measures of SEP

All studies used wealth indices constructed from household assets and other variables to measure SEP per our definition of SEP. Unlike most studies which considered reported SEP in quintiles, quartiles and tertiles for wealth index, some studies also considered SEP as a continuous variable [18, 19, 25, 30, 31, 39, 46, 47, 51, 57], wealth percentiles [23, 48], or as a dichotomous variable [50].

Measures of outcome: malaria

Malaria was assessed as the prevalence or incidence of *Plasmodium* infection**.** Twenty-six studies used microscopy to test for malaria, 12 used rapid diagnostic tests (RDTs), 2 used polymerase chain reaction (PCR) and 1 performed histopathology for diagnosis of placental malaria (Table 1).

Associations between SEP and malaria (regression and mediation analyses)

Most studies employed multivariable logistic regression, followed by Poisson regression. Two studies conducted three mediation analyses. Overall, 39 studies indicated a protective effect of higher SEP on malaria (point effect estimate). Of these, all cross-sectional studies, eight out of nine cohort/case-control studies, and one trial indicated a protective effect. The analyses performed, the effect estimates of SEP on malaria, the confounders adjusted form and quality ratings are shown in Table 2 and Figs. 3 and 4.

Mediators and mediation methods: association between SEP and malaria

Two studies (a cohort and cross-sectional) investigated putative mediating factors on the path from SEP to malaria. Three pathways were explored: access to health- care (use of antimalarials) [46], housing quality, and food security [1]. Only one study had a theoretical framework for mediation analysis [1], and no study assessed for interactions or performed sensitivity analyses which are vital to verify findings. Approaches to mediation analy- sis that overcome the limitations of the difference and the product methods exist and should be used. Details of mediators and methods applied are reported below.

Antimalarial use In a cross-sectional study by de Glanville et al. [46], there was significantly increased use of antimalarials by individuals in wealthier households with relatively lower malaria risk. This study indicated minimal mediation by antimalarial use, although the proportion of the effect mediated was not shown. In the adjusted model, however, both socioeconomic index ($OR = 0.76$, 95% CI 0.66–0.87) and recent antimalarial use ($OR = 0.67$, 95% CI 0.46–0.96) were protective against malaria. In this study, the mediation method applied was a regression-based comparison of the models (assessing for attenua- tion of coefficients) upon inclusion of the mediators.

Housing quality and food security A prospective cohort study by Tusting et al. [1] explored the mediating role of housing and food security on the effect of SEP on malaria incidence in Uganda using the Monte Carlo simula- tion approach described by Imai [59]. Food security was defined as secure if a household had 3–7 days of meat in the menu compared to only 0–2 times. A theoretical framework guided the mediation analysis in Tusting's study [1]. In their analysis, housing type explained 24.9% of the effect of SEP, while food security explained 18.6% of the total effect of SEP on malaria risk.

Health expenditure (used as a proxy for treatment-seeking behaviour) was also explored. Due to limited information (data available for only 57% of children), mediation analysis was not robust and reported no mediating role.

Potential mediators in adjusted regression models involving SEP and malaria

Without performing a formal mediation analysis, several studies adjusted for factors that potentially mediate the SEP and malaria relationship. In these studies, SEP was either a covariate or primary independent variable (expo- sure). These factors satisfy at least two conditions [i.e. (1) have statistically significant relationship between expo- sure (X) and outcome (Y) in univariable regressions and (2) inclusion of the mediator variable (M) should reduce the direct effect of X on Y] to support mediation, according to Baron and Kenny [60] and warrant testing for the mediating role in future studies.

Use of insecticide-treated mosquito nets

The review identified 26 studies which adjusted for ownership/use of ITNs in the association between SEP and malaria. Of these, 20 studies showed a protective effect on malaria among individuals that used mosquito nets compared to those that did not. Two studies [24, 42] found that ITNs were associated with a higher risk of malaria, while four studies [19, 44, 48, 51] found marginal or no association with malaria risk.

Education attainment

Educational attainment refers to the highest level of education that a person has successfully completed. This includes no formal education, primary/elementary, secondary and tertiary or vocational. Eighteen studies that included educational level [categorized into three levels: none, primary, post primary (11 studies), four levels:

Table 1 The characteristics of included studies in the present review

Author year; country	Study design	Study population	Sample size, *n*	Indicator of SEP	Outcome measurement
Siri 2010; Kenya	Case-control	Cases were children less than 10 years with a hemoglobin level < 8 g/dL and parasite density ≥ 10,000/µl and are normal residents	906	Wealth Index (continuous)	Malaria examined by microscopy
Coleman et al. 2010; South Africa	Case-control	All Household members (household considered instead of individuals)	212	Wealth Index (quartile)	Malaria examined by microscopy
Loha et al. 2012; Ethiopia	Cohort	All residents in the Kebele were taken as study subjects. Every household was visited weekly, looking for febrile cases	8121	Wealth Index (continuous)	Malaria RDT
Clark et al. 2008; Uganda	Cohort	Children aged 1–10 years presenting with fever episode	601	Wealth Index (quartile)	Malaria examined by microscopy
Snyman et al. 2015; Uganda	Cohort	HIV-exposed and unexposed children of age 4–6 months	515	Wealth Index (tertiles)	Malaria examined by microscopy
Tusting et al. 2016; Uganda	Cohort	All children aged 6 months to 10 years and their primary caregivers	333	Wealth Index (tertile)	Malaria examined by microscopy
Wanzirah et al. 2015; Uganda	Cohort	All children aged 6 months to 10 years	878	Wealth Index (tertile)	Malaria examined by microscopy
Asante et al. 2013; Ghana	Cohort	Infants of mothers enrolled during pregnancy	1855	Wealth Index (quintile)	Malaria RDT and Malaria examined by microscopy
Vincenz et al. 2022; Mali	Cohort	Mothers who were participants in a cohort study	249 mothers	Wealth z scores	Placental malaria (histology)
Haji et al. 2016; Ethiopia	Cross-sectional	All children under 16 years with symptoms consistent with malaria	830	Wealth Index (tertiles)	Malaria examined by microscopy
Kabaghe et al. 2017; Malawi	Cross-sectional	Children 6–59 months enrolled	1016	Wealth index (continuous)	Malaria RDT
Mathanga et al. 2015; Malawi	Cross-sectional	Pupils enrolled in classes 1–8 of participating schools	2667	Wealth Index (quintiles)	Malaria examined by microscopy
Sakwe et al. 2019; Cameroon	Cross-sectional	Children aged 6 months to 10 years and of both sexes, after full informed consent	362	Development Index)—(continuous)	Malaria examined by microscopy
Skarbinski et al. 2011; Malawi	Cross-sectional	All household members were asked to participate	6581	Wealth Index (quintiles)	Malaria examined by microscopy
Skarbinski et al. 2012; Malawi	Cross-sectional	All household members were asked to participate	884	Wealth Index (quintiles)	Malaria was examined by microscopy
Somi et al. 2007; Tanzania	Cross-sectional	Children and adults	7657	Wealth Index (continuous)	Malaria was examined by microscopy
Somi 2008; Tanzania	Cross-sectional	General population	2034	Wealth index (continuous)	Malaria was examined by microscopy

Table 1 (continued)

Author year; country	Study design	Study population	Sample size, *n*	Indicator of SEP	Outcome measurement
Ssempiira et al. 2017; Uganda	Cross-sectional	Women 15–49 years, Children less than 5 years	4591 children	Wealth Index (quintiles)	Malaria RDT
Temu et al. 2012; Mozambique	Cross-sectional	Children 1–15 years	8338 children	Wealth Index (quartiles)	Malaria RDT
Zoungrana et al. 2014; Burkina Faso	Cross-sectional	All children 0–5 years who had been diagnosed with clinical malaria or produced a paraclinical assessment	510	Wealth Index (dichotomous)	Malaria RDT or Malaria examined by microscopy
Graves et al. 2009; Ethiopia	Cross-sectional	Children and women	11,437	Wealth Index (continuous)	Malaria RDT
Mmbando et al. 2011; Tanzania	Cross-sectional	children 0–19 years	12,298	Wealth Index (tertile)	Malaria examined by microscopy
Siri, 2014; 9 SSA countries	Cross-sectional	Children	34,139	Wealth Index (continuous)	Malaria RDT and Malaria examined by microscopy
Custodio et al. 2009; Equatorial Guinea	Cross-sectional	Children 0–5 years old	552	Wealth Index (tertile)	Malaria examined by microscopy
de Beaudrap et al. 2011; Uganda	Cross-sectional	Children 0–5 years old	2847	Wealth Index (continuous)	Malaria RDT and Malaria examined by microscopy
Sonko et al. 2014; The Gambia	Cross-sectional	Children and the general population	6–59 months ($n = 1248$), 5 to 14 years ($n = 1987$), adults ($n = 2306$)	Wealth Index (quintile)	Malaria RDT and Malaria examined by microscopy
Chirombo et al. 2014; Malawi	Cross-sectional	Children under 5 years	2093	Wealth Index (quintiles)	Malaria RDT
de Glanville et al. 2019; Kenya	Cross-sectional	Individuals older or equal to 5 years	2113	Wealth Index (continuous)	Malaria examined by microscopy
Florey et al. 2012; Kenya	Cross-sectional	Children aged 8–17 and adults 18–86	223 children and 338 adults	Wealth index (continuous)	Polymerase chain reaction
Kahabuka et al. 2012; Tanzania	Cross-sectional	Caretakers who brought their sick children at Korogwe and Muheza district hospitals	296	Wealth Index (tertiles)	Malaria RDT
Ma et al. 2017; DRC	Cross-sectional	Healthy children aged 2 months to 5 years attending well-child and/or immunization visits	647	Wealth index (continuous)	Malaria RDT
West et al. 2013; Tanzania	Cross-sectional	Children 6–14 years	5152	Wealth index (cluster SEP) (tertiles)	Malaria RDT
Williams et al. 2016; Burkina Faso, The Gambia, Ghana and Mali	Cross-sectional	Women enrolled in a trial of intermittent screening and treatment of malaria in pregnancy (ISTP) versus IPTP	2526	Wealth Index (quintiles)	Malaria RDT and Polymerase Chain Reaction
Zgambo et al. 2017; Malawi	Cross-sectional	Children under the age of five	2012 Survey ($n = 2173$), 2014 Survey ($n = 2029$)	Wealth index (quintiles)	Malaria examined by microscopy
Mann et al. 2021; Nigeria	Cross-sectional	Children aged 6–59 months	12,996	Wealth index (quintile)	Malaria examined by microscopy
Emina et al. 2021; DRC	Cross-sectional	Children aged 6–59 months	8547	Wealth index (quintile)	Malaria examined by microscopy
Mwaiswelo et al. 2021; Tanzania	Cross-sectional	Children aged 3–59 months	2340	Wealth index (tertiles)	Malaria RDT

Table 1 (continued)

Author year; country	Study design	Study population	Sample size, *n*	Indicator of SEP	Outcome measurement
Mangani et al. 2022; Malawi	Cross-sectional	All individuals aged 6 months or older who slept in the house for at least 2 weeks of the previous month	5829	Wealth Index (quintiles)	Malaria RDT
Ejigu 2020; Mozambique	Cross-sectional	Children of age 6-59 months	4347	Wealth Index (quintiles)	Malaria RDT
Gari et al. 2016; Ethiopia	Trial	General population	5309	Wealth Index (tertiles)	Malaria RDT or Malaria examined by microscopy
Liu et al. 2014; Tanzania	Trial	Children (one per household) were followed from 2 to 24 months	435	Wealth Index (quintiles)	Malaria examined by microscopy

DRC Democratic Republic of Congo, *IPTP* intermittent preventive treatment in pregnancy, *RDT* rapid diagnostic test, *SEP* socioeconomic position

Table 2 Studies on socioeconomic position (SEP) and malaria with analysis approaches

Author year	Analyses performed	Risk estimate (95% *CI*) and result of mediation (if any)	Adjusted for confounders/mediators	Quality score
Siri 2010	Multivariable logistic regression	*OR*. wealth percentile [0.8 (0.7-0.9)]	ITN use, mosquito coils, age, location, gender of HH head	Strong
Coleman et al. 2010	Multivariable negative binomial regressions	*OR*. Reference (the 1st quartile) third [0.24 (0.09-0.65)], and fourth (least poor) [0.27 (0.10-0.79)]	Housing structure, closing windows on retiring	Strong
Loha et al. 2012	Poisson regression	(*Beta* coefficient = − 0.155, P-value = 0.043)	Age, gender, ITN use, and distance to the breeding place	Strong
Clark et al. 2008	Generalized estimating equations with control for repeated measures	*IRR*. Reference (SEP quartiles 1 and 2 combined). Third [0.83 (0.62-1.10)], fourth [0.77 (0.56-1.04)]	Age, gender, ITN use, distance to the swamp, household crowding	Strong
Snyman et al. 2015	Negative binomial regression models	*IRR*. Reference (lowest). Middle [0.91 (0.76-1.1)], highest [0.86 (0.72-1.03)]	Caregiver's age, education, house construction, location, number of rooms	Moderate
Tusting et al. 2016	Multivariable logistic regression and causal steps approach-simulations and Bootstrapping	*IRR*. Reference (lowest), middle [1.12 (0.90-1.40)], highest [1.05 (0.83-1.34)] Housing type explained 24.9% of the SEP effect, and food security explained 18.6%	Age, gender, level of education, housing type[a], food security[a], distance to facility, household size	Strong
Wanzirah et al. 2015	Multivariable logistic regression and negative binomial regression	*OR*. Reference (1st tertile) Walukuba: 2nd tertile [0.82 (0.38-1.78)], 3rd tertile [0.83 (0.31–2.18)] Kihihi: 2nd tertile [0.54 (0.28-1.06)], 3rd tertile [0.37 (0.20-0.71)] Nagongera: 2nd tertile [0.72 (0.50-1.04)], 3rd tertile [0.71 (0.47-1.07)]	Age, gender, house type, floor material, roof material, eaves	Moderate
Asante et al. 2013	Cox proportional hazards regression	*HR*. Reference (least poor), less poor [1.54 (1.23-1.93)], poor [1.88 (1.50-2.35)], poorer [1.86 (1.50-2.31)], most poor [2.21 (1.77-2.76)]	Housing (thatched roof), location, distance to the health facility, ITN use	Strong
Haji et al. 2016	Multivariable logistic regression	*OR*. Reference (low), medium [1.51 (0.51-4. 45)], high [0.93 (0.35-2.45)]	Location, ITN use, age of the child, gender, sought advice before, knowledge of malaria	Moderate
Kabaghe et al. 2017	Modified Poisson regression	*HPD*. SEP [− 0.07 (− 0.11 to − 0.03)]	Age, ITN use, elevation and Normalized Difference Vegetation Index	Weak
Mathanga et al. 2015	Multivariable logistic regression	*OR*. Reference (poorest), poor [1.08 (0.82-1.42)], medium [1.30, 0.98-1.72)], less poor [1.26 (0.94-1.70)], least poor [0.74 (0.55-0.99)]	Age, gender, ITN use, reported fever, education status, household size, school feeding)	Moderate
Sakwe et al. 2019	Multivariable logistic regression	*OR*. Development Index [0.76 (0.58-0.99)]	Child age, gender, nutrition status, housing type, HH size, HH head education, and caregiver	Moderate
Skarbinski et al. 2011	Multivariable logistic regression	*OR*. Reference (least poor), 4th [2.10 (1.45-3.05)], 3rd [2.64 (1.80-3.87)], 2nd [2.84 (2.03-3.97)], 1st [3.46 (2.30-5.21)]	District, ITN use, IRN use	Weak
Skarbinski et al. 2012	Binomial regression modelling	*OR*. Reference (least poor), 4th [1.19 (0.71-2.00)], 3rd [1.72 (1.09-2.70)], 2nd [1.52 (1.01-2.29)], 1st [1.47 (0.98-2.20)]	IRS use, ITN use, wall material, roof material	Weak
Somi et al. 2007	Probit regression	Coefficients: SEP score based on PCA (numerical) = − 0.04 (*P*-value = 0.012)	ITN use, age, location, knowledge, eaves	Moderate

Table 2 (continued)

Author year	Analyses performed	Risk estimate (95% *CI*) and result of mediation (if any)	Adjusted for confounders/mediators	Quality score
Somi et al. 2008	Probit regression	Coefficients: SEP score based on PCA (numerical) = − 0.074	Age, location, ITN use, HH size, eaves, knowledge	Moderate
Ssempiira et al. 2017	Bayesian geostatistical logistic regression	*OR*. Reference (poorest), richest [0.19 (0.14, 0.27)], richer [0.52 (0.42, 0.61)], medium [0.77 (0.85, 1.15)], poorer [0.86 (0.72, 1.04)]	Location, ITN use, IRS use, age, mothers' education, land surface temperature	Moderate
Temu et al. 2012	Multivariable logistic regression	*OR*. Reference (poorest), 2nd quartile [0.9 (0.7-1.2)], 3rd quartile [0.9 (0.7-1.3)], and 4th quartile [0.5 (0.4-0.7)]	Age, year, ITN use, HH size, house construction, children with current fever	Weak
Zoungrana et al. 2014	Multivariable logistic regression	*OR*. Reference (high) Low SEP [4.11 (1.44, 11.75)]	Age, gender, marital status, education, knowledge, ethnicity, residence, distance, travel time, HH size, decision making	Strong
Graves et al. 2009	Multivariable logistic regression	*OR*. Asset index [0.79 (0.66—0.94)]	Age, gender, altitude, monthly rain, ITN use, IRS use in the last 12 months	Moderate
Mmbando et al. 2011	Muitivariate logistic regression Spatial analysis	*OR*. Reference (high), medium [1.6(1.3-1.9)], low [1.6 (1.4-1.91)]	Age, ITN use, ITN rate, housing, year, altitude	Moderate
Siri 2014	Multilevel logistic regression	*OR*. Wealth percentile [0.990 (0.987-0.992)]	Child age, mother's age, ITN use, country, HH size, location, education, finished windows and ceilings	Moderate
Custodio et al. 2009	Multivariable logistic regression	*OR*. Reference (low), medium [0.97 (0.29-3.25)], high [0.15 (0.05-0.50)]	ITN use, antimalarials use in pregnancy, age, gender	Moderate
de Beaudrap et al. 2011	Multivariable logistic regression	*OR*. SEP score [0.75 (0.64-0.89)]	Child age, weight, housing score, ITN use, education and latitude	Moderate
Sonko et al. 2014	Multivariable logistic regression	For children 6-59 months, *OR*. Reference (poorest), 2nd [0.40 (0.20-0.70], 3rd [0.5 (0.30-0.90)], 4th [0.30 (0.10-0.60), 5th [0.10 (0.04-0.30)] Children 5-14 years 2nd [0.60 (0.30-1.20]), 3rd [0.70 (0.50-1.10]), 4th [0.20 (0.10-0.50)], 5th [0.30 (0.10-0.60)]. For the general population 2nd [0.80 (0.40-1.30)], 3rd [0.80 (0.50-1.20), 4th (0.40 (0.20-0.80), 5th [0.20 (0.07-0.80)]	Housing (wall type, roof type, floor type, window type,) age, gender	Moderate
Chirombo et al. 2014	Structured additive logistic regression (Bayesian approach)	*OR*. Reference (poorest), richest [0.22 (0.14-0.37)], richer (0.42 (0.28-0.64)], medium [0.66 (0.45-0.96)], poorer [1.10 (0.76-1.60)]	ITN use, region, age and location	Weak
de Glanville et al. 2019	Multivariable logistic regression Mediation analysis using a hierarchical approach	*OR*. SEP [0.76 (0.66-0.86)] Minimal mediation by antimalarial use	Gender, age, access to health care (antimalaria use[a])	Moderate
Florey et al. 2012	GEE models with exchangeable correlation matrix and logistic distributions	*OR*. SEP [0.76 (0.54-1.05)]	Outdoor night activity	Weak
Kahabuka et al. 2012	Multivariable logistic regression	*OR*. Reference (high), middle [1.00 (0.40-2.80)], and low [1.20 (0.40-3.70)]	Education, parity, hospital travel time, use of near public health facility, source of the first treatment	Weak

Table 2 (continued)

Author year	Analyses performed	Risk estimate (95% *CI*) and result of mediation (if any)	Adjusted for confounders/mediators	Quality score
Ma et al. 2017	Multivariable logistic regression	*OR*. SEP [1.20 (0.94-1.50)]	Study site, age, HH size, education, HIV Status, ITN use, phone ownership	Moderate
West et al. 2013	Multivariable logistic regression	*OR*. Reference (poorest), mild [0.69 (0.34-1.40)], least poor [0.13 (0.05-0.34)]	HH spaying, cluster ITN coverage, age	Moderate
Williams et al. 2016	Multivariable logistic regression	*OR*. Reference (wealthiest), wealthy [1.82 (0.68-4.83)], medium [0.96 (0.18-5.02)], poor [6.48 (1.68, 25.0), poorest [6.55 (1.27-33.70)]	Education, age, gestation age, gravidity, country	Weak
Zgambo et al. 2017	Multivariable logistic regression	*OR*. Reference (richest), 2012 survey: poorest [2.90 (1.60-5.30)], poorer [2.3 (1.10-4.60)], middle [2.50 (1.30-5.00)], richer [1.9 (1.10-3.60)] 2014 survey: poorest [4.7 (1.3-16.2)], poorer [2.9 (0.9-10.0)], middle [2.7 (0.7-10.2)], richer [1.9 (0.4-8.0)]	ITN use, ITN ownership, IRS, region, location, Gender, child age, altitude, and education of the mother	Moderate
Gari T et al. 2016	A multilevel mixed effects Poisson regression	*IRR*. Reference (rich). Poor [0.94 (0.35-2.45)], medium [0.70 (0.33-1.50)]	Age, gender, HH head education, ITN use	Strong
Liu et al. 2014	Multivariable negative binomial regressions	*IRR*. Reference (middle). Poorest [1.316 (0.915-1.891)], poorer [1.292 (0.876-1.905)], richer [1.090 (0.667-1.782)], richest [1.059 (0.533-2.103)]	Age, housing index, regular repellent use, ITN use, location, water source, electricity	Strong
Vincenz et al. 2022	GEE for binary logistic regression	*OR*. [1.37 (0.99-1.91)]	Maternal age, gravidity, IPTP use, education, season	Weak
Mann et al. 2021	Multivariable logistic regression	*OR*. Reference (richest), poorest [4.60 (3.05-6.96)], poorer [4.18 (2.81-6.19)], middle [3.27 (2.26-4.71)], richer [2.23 (1.55-3.21)]	Age, gender, residence, education, nutrition (stunting)	Moderate
Emina et al. 2021	Generalized estimating equations with control for repeated measures	*OR*. Reference (poorest), poorer [1.20 (0.95-1.52)], middle [1.00 (0.77-1.31)], richer [0.69 (0.50-0.96)], richest [0.19 (0.10-0.37)]	Gender, child's age, mother education, ITN use, sex of HH head, type of residence, province of residence	Moderate
Mwaiswelo et al. 2021	Multivariable logistic regression	*OR*. Reference (low). Medium [0.54, 0.36-0.83)], upper [0.41(0.25-0.66)]	ITN ownership, HH size, education, district (location)	Weak
Mangani et al. 2022	Multilevel logistic regression	*OR*. Reference (poorest), poorer [0.80 (0.65-1.00)], middle [0.74 (0.56-0.99)], richer [0.80 (0.62-1.01)], richest [0.64 (0.50-0.81)]	HH wall, roof materials, education, ITN use, child's age, gender, distance from the irrigation scheme	Moderate
Ejigu 2020	Geostatistical logistic model	*OR*. Reference (poorest), poorer [0.99 (0.80-1.25)], middle [0.67 (0.53-0.85)], richer [0.52 (0.40-0.69)], richest [0.19 (0.11-0.31)]	Province, mothers' education, anemia, ITN use, age in months, ITN coverage, malaria incidence	Weak

CI confidence interval, *GEE* generalized estimating equations, *HH* household, *HPD* highest posterior density, *PCA* principal component analysis, *OR* odds ratios, *IRR* incidence rate ratios, *ITN* insecticide treated net, *IRS* indoor residual spraying

[a] Mediators assessed in formal analyses

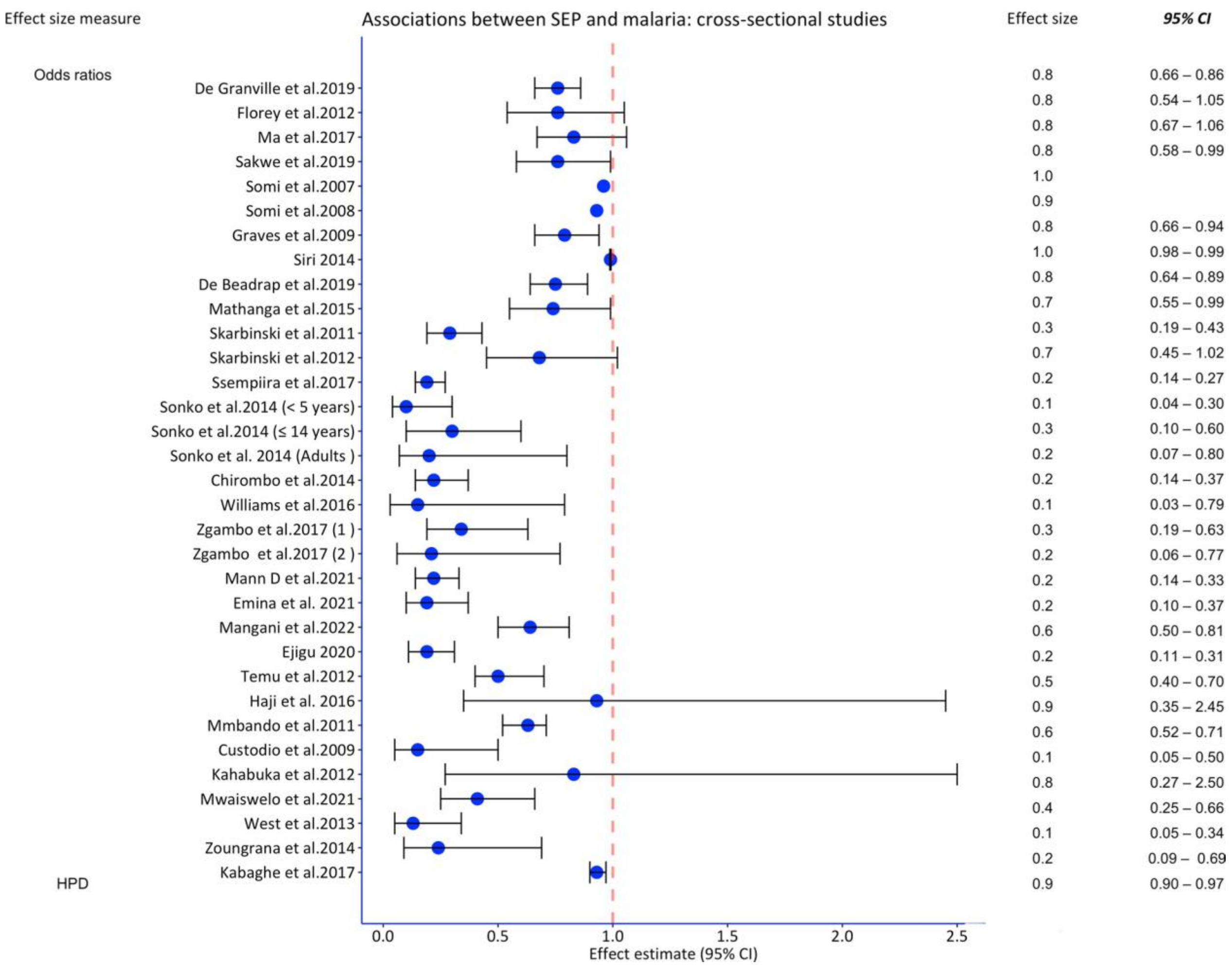

Fig. 3 Forest plot of risk estimates from cross-sectional studies assessing the association between socioeconomic position and malaria in Sub-Saharan Africa. *CI* confidence interval, *HPD* highest posterior density, *SEP* socioeconomic position

none, primary, secondary, post primary (4 studies), two levels: none/primary, post primary (3 studies)], and SEP in models predicting malaria risk were identified. The effect of educational level on malaria risk was mixed with 12 studies [28, 33, 34, 37, 40–42, 51–53, 56, 57] indicating the protective effect of higher educational levels on malaria risk, and six studies [23, 25, 44, 49, 50, 54] showed no significant association with malaria.

Housing quality

Housing was expressed based on quality of specific housing materials (good vs poor); walls (n = 5), roof (n = 5), windows (n = 2), floor (n = 1), or additive housing index (n = 3). Eleven studies included housing quality in the multivariable regression models involving the association between SEP and the prevalence or incidence of malaria. Although eight studies [20, 21, 25–27, 29, 41, 43] indicated a significant protective effect of housing on malaria risk after controlling for SEP, the remaining two studies showed no associations between housing and malaria [23, 57]. There were also mixed associations in the cross-sectional survey by Somi [30], where improved walls were associated with reduced odds of malaria, while improved roofs had no significant effect on the risk of malaria. Rather than looking at the independent effect of roofs, walls, windows, eaves, and ceilings on malaria, most studies assessed the combined effect of these struc- tures. Using these structures, studies grouped houses as poor quality (thatched roofs, dirt floors, completely uncovered windows, no ceilings, rough or mud walls and open eaves) and high quality (iron/tile roofs, concrete/ brick walls, closed eaves, screened windows and ceilings).

Indoor residual spraying

The review identified five studies that adjusted for IRS in their multivariable models containing SEP. Of these,

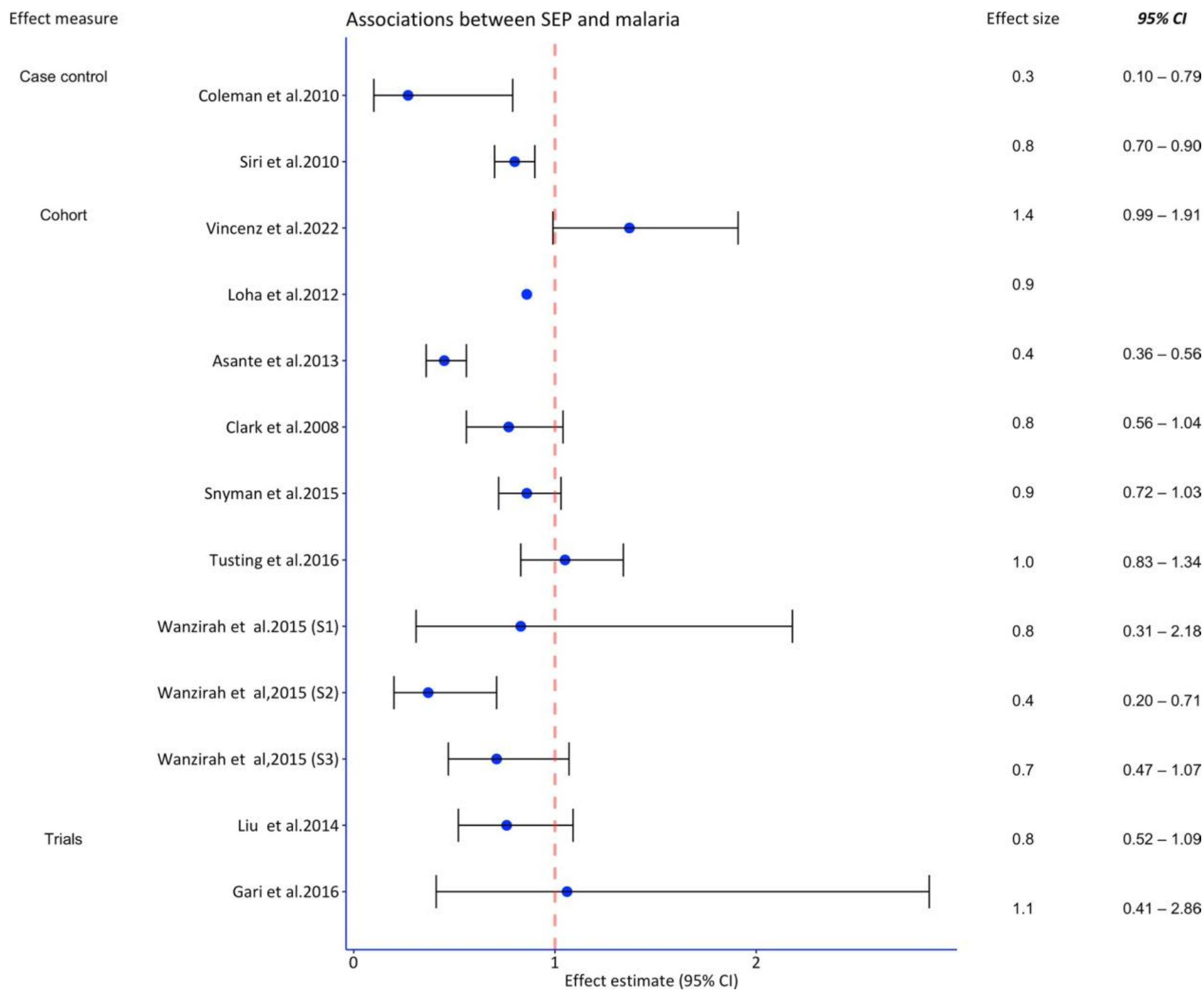

Fig. 4 Forest plot of risk estimates from the cohort, case-control studies and trials for the association between socioeconomic position and malaria in Sub-Saharan Africa. *CI* confidence interval, *SEP* socioeconomic position

four studies showed that IRS was associated with a lower risk of malaria [32, 35, 36, 42]. Graves et al. [19] did not find a relationship between IRS and malaria risk whether assessed at a 6- or 12-month history of IRS.

Health-seeking behaviour

Access to health care was defined in terms of choice of place for healthcare (facility vs home; far vs near- est facility), and duration between symptom onset and seeking of care. Three studies adjusted for self-reported health-seeking behaviours in their associations involv- ing SEP and malaria prevalence [28, 45, 50]. Two stud- ies showed that seeking facility care versus at-home care and receiving treatment for fever symptoms promptly reduced the risk of severe malaria [28, 50]. In contrast, a study in Ethiopia found no significant asso- ciation between early treatment seeking and malaria risk [45]. It is important to note that these studies used different proxies of health-seeking behaviour, and outcomes were different for example in one study, the outcome was severe malaria and in another, it was uncomplicated malaria.

Antimalarials, nutrition status and outside night activity

The review identified two studies that adjusted for anti-malarials [24, 54], four that adjusted for nutritional status [24, 34, 54, 57], and one trial that controlled for repellent use [29]. All these studies highlighted the pro-tective effect of antimalarial use, nutrition, and repel-lent use, respectively. In addition, one cross-sectional study showed no association between outdoor night activities and malaria [47].

Quality of reviewed studies

Eligible studies were assessed for their methodological quality using the EPHPP tool. Eight (8) studies were rated as having high quality (strong), and 11 studies were rated as having low quality, with the majority of the included studies having a moderate methodological quality ($n = 22$). Eight of the included studies deemed confound- ing bias to be a serious threat. These studies only controlled for less than 60% of the significant confounders in the association between SEP and malaria. Six (6) studies were found to have selection bias, and 30 of the 41 studies were cross-sectional, making the claim of mediation only speculative (Additional file 1: Table S4).

Discussion

This systematic review aimed to identify, summarize and critically appraise the existing evidence regarding the variables that potentially mediate the relationship between SEP and malaria in SSA. Our review shows that evidence of mediating pathways between household SES and malaria is sparse and under-researched.

Of the 41 studies, only two assessed mediators of the SEP and malaria path using formal mediation analyses specifically housing quality, food security, antimalarial use. One study showed that a proportion of the total effect of SEP on malaria was mediated through housing and food security, while another showed minimal mediation by antimalarial use. However, each mediator was only investigated in one study, meaning these findings remain inconclusive. Other studies indicated that ITN use, higher education, better nutrition, housing quality, IRS, and repellent use could, to a great extent, protect against malaria. These, however, did not conduct mediation analyses but included potential mediators as covariates. This review provides valuable insights for directed action/interventions to alleviate poverty-related malaria burdens, improve health outcomes of marginalized populations, and contribute to reducing global malaria incidence and mortality rates by at least 90%, as per the global technical strategy for malaria [61] and in line with the Sustainable Development Goals (SDGs), particularly the goal of ending poverty (SDG 1) and achieving univer- sal health coverage (SDG 3). For instance, based on these findings, interventions that target housing improvements and food security could substantially prevent /mitigate malaria risk. It is important to acknowledge that the measurement of SEP varied across different studies and countries, particularly in terms of the included assets, data reduction techniques, and the decision to categorize or not which significantly impacts the comparability of findings, even when there is consistency in the direction of the association between SEP and malaria. We also acknowledge that SEP may have improved or declined in the study areas however all studies (except one) were published within 10 years since recruitment which makes findings relevant.

Mediators identified through formal mediation

Our review indicates that housing quality and food security could mediate socioeconomic differences in malaria risk. One cohort study demonstrated that housing qual- ity and food insecurity mediated 24.9% and 18.6% of the effect of SEP on malaria incidence in SSA, respec- tively [1]. The study also suggested that treatment-seek- ing behavior could have a mediating role; however, the authors did not perform a robust mediation analysis due to insufficient sample size. The analyses in Tusting's paper [1] were informed by a conceptual framework that, although commendable, did not operationalize pathways such as access to healthcare and ITNs in their mediation analyses. In another study [46], antimalarial treatment was also found to mediate the association between SEP and malaria. Yet, this study did not provide information on the percentage of total effect mediated and the identi- fiability assumptions checked, hence requiring a cautious interpretation of the findings [46]. These assumptions are (i) No unmeasured exposure-outcome confounding given covariates, C, (ii) No unmeasured mediator-outcome confounding given C, (iii) No unmeasured exposure-mediator confounding given C, (iv) No effect of expo- sure that confounds the mediator-outcome relationship [14]. The proportion of the socioeconomic differences in malaria mediated by housing and food security was small (less than 30%), which indicated that other potential mediators could explain part of the effect of SEP. Nev- ertheless, incremental improvements in housing qual- ity and interventions, such as irrigation and agriculture could promote food security, thereby protecting against malaria.

While previous literature suggests the mediating role of socioeconomic and structural factors in the associa- tion between SEP and malaria, research remains limited. Some assumptions for mediation were not always met (including potential reverse causality and identifiabil- ity), and many analyses do not consider interactions nor adjust for mediator outcome confounding, which raises concerns about the validity of the mediation effects reported. Future studies need to apply more robust anal- yses on longitudinal data for which many assumptions may hold.

Potential mediators (with no formal mediation)

Rather than formal mediation analysis, variables were considered potential mediators if their inclusion in the adjusted models resulted into change (reduction) in the SEP coefficient. While it is generally not recommended to control for mediating variables in the causal relationship because conditioning on them introduces bias [62], the attenuation in coefficients of SEP in a multivariable model implies they could be mediators.

Most studies in this review indicated a protective effect on malaria with higher education [28, 34, 37, 41, 42, 51, 57], IRS [32, 35, 36, 42], better housing [20, 21, 25–27, 29, 41, 43], and use of ITNs after adjusting for SEP. Consistent with previous literature, which shows a consistent association between wealth and ITN use and IRS [63–66], a recent systematic review of the effectiveness of ITNs showed a strong protective effect against malaria [67]. In another review, the addition of IRS on averaged reduced malaria parasite prevalence ($RR = 0.61$, 95% CI 0.42 to 0.88) [68] indicates that interventions targeting IRS and ITNs combined may significantly affect malaria morbidity although this effect may not be observed in all contexts. It is important to note that utilization of IRS and ITNs may be affected by their high costs, low coverage and poor quality of IRS in some settings [69].

Educational attainment is also a well-known predictor of malaria risk [6]. Greater wealth encourages higher educational attainment [70], which may increase individuals' knowledge of prevention and treatment, decision-making, and access to information [58]. This could encourage the uptake of preventive measures and consequently lower malaria risk. In our review, 12 of 18 studies indeed found an association between higher educational attainment and a lower risk of malaria after adjusting for SEP. However, the evidence regarding the proportion of SEP effect mediated through education is limited.

Further, most studies that adjusted for housing quality found that improved housing was protective against malaria with a reduced coefficient of SEP. Higher SEP makes it easier to acquire better housing (shelters with better roofs, shutters, and eaves), which can then reduce exposure to the biting *Anopheles* at night by preventing the entry of mosquito vectors. Evidence for the effect of SEP mediated through housing is still forthcoming, with a single study suggesting that improvements in housing could partly explain the protective effect of SEP [1]. In light of this evidence, improving housing or improving accessibility of building materials to households with low SEP could contribute to reduction of malaria burden. However, there is a need to determine potential mediators and their relative contributions to the association between SEP and malaria to inform the design and implementation of targeted socio-structural interventions against malaria.

Strengths, limitations and implications for further research

To the best of our knowledge, this is the first systematic review that has attempted to explore the potential mediators on the path between SEP and malaria in SSA. Unlike recent reviews [4, 6], which included education and housing as proxies for SEP, we defined our exposure (SEP) based on household wealth indices (asset-based indices), which is a more reliable measure of household wealth in low-income countries. However, the review's findings are not without limitations. First, while the review was comprehensive and involved 41 articles and tens of thousands of participants, we identified only three formal mediation analyses of pathways linking SEP and malaria; hence, uncertainties remain around the relative contribution of several potential mediators. Second, we may have missed other studies because we searched only two databases and also did not search grey literature or studies in languages other than English. Nevertheless, we think this is still a specialized area of academic research, and most of the studies that meet the criteria are most likely to be published in international peer-reviewed journals. Thirdly, most studies had methodological limitations, such as the lack of a conceptual framework, sensitivity analyses, ignorability assumptions, and the use of cross-sectional data, which renders claims of causal mediation speculative because temporarity could not be established. Longitudinal designs are better suited to demonstrate temporality, a key aspect in causal inferences and especially important for studies on SEP and malaria due to the bi-directionality of their relationship [30]. With longitudinal data, more suitable methods, such as VanderWeele's parametric mediational g-formula, can account for time-varying exposures, mediators and confounding affected by previous exposure could be applied [71].

Conclusions

Our study indicates that a relatively small body of research has tested indirect pathways between SEP and malaria. From reviewed evidence, extant research suggests that housing, food security and recent antimalarial use are likely mediators in the SEP-malaria relationship in SSA. Although other pathways, such as education, IRS and ITN use, nutrition, and health-seeking behaviour, are not fully supported by current evidence, their role cannot be ignored due to their demonstrated protective effect on malaria when modelled with SEP as a covariate. More formal mediation analyses using longitudinal data are needed to overcome methodological limitations, such as cross-sectional data, insufficient confounder adjustment, and limited use of sound conceptual frameworks.

This research area holds much potential in informing the design of more effective interventions for malaria control.

Abbreviations

DRC	Democratic Republic of Congo
EPHPP	Effective Public Health Practice Project Tool
GEE	Generalized estimating equations
HH	Household
HPD	Highest posterior density
IPTP	Intermittent preventive treatment in pregnancy
IRS	Indoor residual spraying
IRR	Incidence rate ratios
ITN	Insecticide treated Nets
OR	Odds ratios
RDT	Rapid diagnostic test
PCA	Principal Component Analysis
SEP	Socioeconomic position
SSA	Sub-Saharan Africa

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40249-023-01110-2.

Additional file 1: Table S1. Highlights of the review. **Table S2.** Detailed search strategy, conducted on May 31, 2022. **Table S3.** Quality assessment tool for quantitative studies. **Table S4.** Assessment of the quality of included studies.

Acknowledgements

We acknowledge the Infectious Epidemiology Department at Bernhard Nocht Institute for Tropical Medicine for their cooperation and support towards completing this article.

Author contributions

JB, DIP, EL and STW conceived the study. THH, MAF and STW spearheaded the review, including conducting database searches, screening review articles, updating the review and critically appraising articles. STW drafted the manuscript, which was critically reviewed by JB, JM, EL and DIP. EL, JB, DIP and JM provided support and mentorship during the development and writing of the review. All authors read and approved the final manuscript.

Funding

Open Access funding enabled and organized by Projekt DEAL.

Availability of data and materials

All data relevant to the study are included in this published article and uploaded as Additional file.

Declarations

Ethics approval and consent to participate

This research did not require institutional review approval since all data were publicly available and collected from existing online databases. This research did not involve any human subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 12 December 2022 Accepted: 29 May 2023
Published online: 08 June 2023

References

1. Tusting LS, Rek J, Arinaitwe E, Staedke SG, Kamya MR, Cano J, et al. Why is malaria associated with poverty? Findings from a cohort study in rural Uganda. Infect Dis Poverty. 2016;5:78.
2. WHO. World malaria report 2020: 20 years of global progress and challenges. WHO. 2020. https://apps.who.int/iris/rest/bitstreams/1321872/retrieve. Accessed 8 Apr 2022.
3. Teklehaimanot, PaolaMejia A. Malaria and poverty. Ann N Y Acad Sci. 2008;1136:32–7.
4. Tusting LS, Willey B, Lucas H, Thompson J, Kafy HT, Smith R, et al. Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis. Lancet. 2013;382:963–72.
5. Tusting LS, Ippolito MM, Willey BA, Kleinschmidt I, Dorsey G, Gosling RD, et al. The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. Malar J. 2015;14:209.
6. Degarege A, Fennie K, Degarege D, Chennupati S, Madhivanan P. Improving socioeconomic status may reduce the burden of malaria in sub Saharan Africa: a systematic review and meta-analysis. PLoS ONE. 2019;14:e0211205.
7. Krefis AC, Schwarz NG, Nkrumah B, Acquah S, Loag W, Sarpong N, et al. Principal component analysis of socioeconomic factors and their association with malaria in children from the Ashanti Region, Ghana. Malar J. 2010;9:201.
8. Falkingham J, Namazie C. Measuring health and poverty: a review of approaches to identifying the poor. DFID. 2002. https://assets.publishing.service.gov.uk/media/57a08d46ed915d622c0018bd/Measuring-health-and-poverty.pdf. Accessed 17 Sept 2021.
9. Filmer D, Pritchett LH. Estimating wealth effects without expenditure data-or tears: an application to educational enrollments in states of India. Demography. 2001;38:115–32.
10. Fobil JN, Kraemer A, Meyer CG, May J. Neighborhood urban environmental quality conditions are likely to drive malaria and diarrhea mortality in Accra, Ghana. J Environ Public Health. 2011;2011: 484010.
11. Barat LM, Palmer N, Basu S, Worrall E, Hanson K, Mills A. Do malaria control interventions reach the poor? A view through the equity lens. Am J Trop Med Hyg. 2004;71:174–8.
12. Liu J. Early health risk factors for violence: conceptualization, review of the evidence, and implications. Aggress Violent Behav. 2011;16:63–73.
13. MacKinnon DP. Introduction to statistical mediation analysis. London: Routledge; 2012.
14. VanderWeele TJ. Mediation analysis: a practitioner's guide. Annu Rev Public Health. 2016;37:17–32.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8:336–41.
16. World Bank. Sub-Saharan Africa. 2022. https://data.worldbank.org/region/sub-saharan-africa. Accessed 20 June 2020.
17. Thomas H, Ciliska D, Micucci S, Wilson-ABra J, Dobbins M. Effective public health practice project (EPHPP). 1999.
18. Loha E, Lindtjørn B. Predictors of *Plasmodium falciparum* malaria incidence in Chano Mille, South Ethiopia: a longitudinal study. Am J Trop Med Hyg. 2012;87:450–9.
19. Graves PM, Richards FO, Ngondi J, Emerson PM, Shargie EB, Endeshaw T, et al. Individual, household and environmental risk factors for malaria infection in Amhara, Oromia and SNNP regions of Ethiopia. Trans R Soc Trop Med Hyg. 2009;103:1211–20.
20. Coleman M, Coleman M, Mabaso ML, Mabuza AM, Kok G, Coetzee M, et al. Household and microeconomic factors associated with malaria in Mpumalanga, South Africa. Trans R Soc Trop Med Hyg. 2010;104:143–7.

21. Mmbando BP, Kamugisha ML, Lusingu JP, Francis F, Ishengoma DS, Theander TG, et al. Spatial variation and socio-economic determinants of *Plasmodium falciparum* infection in northeastern Tanzania. Malar J. 2011;10:145.
22. Clark TD, Greenhouse B, Njama-Meya D, Nzarubara B, Maiteki-Sebuguzi C, Staedke SG, et al. Factors determining the heterogeneity of malaria incidence in children in Kampala, Uganda. J Infect Dis. 2008;198:393–400.
23. Siri JG. Independent associations of maternal education and household wealth with malaria risk in children. Ecol Soc. 2014;19:33.
24. Custodio E, Descalzo MA, Villamor E, Molina L, Sánchez I, Lwanga M, et al. Nutritional and socio-economic factors associated with *Plasmodium falciparum* infection in children from Equatorial Guinea: results from a nationally representative survey. Malar J. 2009;8:225.
25. De Beaudrap P, Nabasumba C, Grandesso F, Turyakira E, Schramm B, Boum Y 2nd, et al. Heterogeneous decrease in malaria prevalence in children over a six-year period in south-western Uganda. Malar J. 2011;10:132.
26. Asante KP, Owusu-Agyei S, Cairns M, Dodoo D, Boamah EA, Gyasi R, et al. Placental malaria and the risk of malaria in infants in a high malaria transmission area in Ghana: a prospective cohort study. J Infect Dis. 2013;208:1504–13.
27. Sonko ST, Jaiteh M, Jafali J, Jarju LBS, D'Alessandro U, Camara A, et al. Does socio-economic status explain the differentials in malaria parasite prevalence? Evidence from The Gambia. Malar J. 2014;13:449.
28. Kahabuka C, Kvåle G, Hinderaker SG. Factors associated with severe disease from malaria, pneumonia and diarrhea among children in rural Tanzania—a hospital-based cross-sectional study. BMC Infect Dis. 2012;12:219.
29. Liu JX, Bousema T, Zelman B, Gesase S, Hashim R, Maxwell C, et al. Is housing quality associated with malaria incidence among young children and mosquito vector numbers? Evidence from Korogwe, Tanzania. PLoS ONE. 2014;9: e87358.
30. Somi MF, Butler JR, Vahid F, Njau J, Kachur SP, Abdulla S. Is there evidence for dual causation between malaria and socioeconomic status? Findings from rural Tanzania. Am J Trop Med Hyg. 2007;77:1020–7.
31. Somi MF, Butler JR, Vahid F, Njau JD, Kachur SP, Abdulla S. Use of proxy measures in estimating socioeconomic inequalities in malaria prevalence. Trop Med Int Health. 2008;13:354–64.
32. West PA, Protopopoff N, Rowland M, Cumming E, Rand A, Drakeley C, et al. Malaria risk factors in North West Tanzania: the effect of spraying, nets and wealth. PLoS ONE. 2013;8: e65787.
33. Mwaiswelo RO, Mmbando BP, Chacky F, Molteni F, Mohamed A, Lazaro S, et al. Malaria infection and anemia status in under-five children from Southern Tanzania where seasonal malaria chemoprevention is being implemented. PLoS ONE. 2021;16: e0260785.
34. Mathanga DP, Halliday KE, Jawati M, Verney A, Bauleni A, Sande J, et al. The high burden of malaria in primary school children in Southern Malawi. Am J Trop Med Hyg. 2015;93:779–89.
35. Skarbinski J, Mwandama D, Luka M, Jafali J, Wolkon A, Townes D, et al. Impact of health facility-based insecticide treated bednet distribution in Malawi: Progress and challenges towards achieving universal coverage. PLoS ONE. 2011;6: e21995.
36. Skarbinski J, Mwandama D, Wolkon A, Luka M, Jafali J, Smith A, et al. Impact of indoor residual spraying with lambda-cyhalothrin on malaria parasitemia and anemia prevalence among children less than five years of age in an area of intense, year-round transmission in Malawi. Am J Trop Med Hyg. 2012;86:997–1004.
37. Zgambo M, Mbakaya BC, Kalembo FW. Prevalence and factors associated with malaria parasitaemia in children under the age of five years in Malawi: a comparison study of the 2012 and 2014 Malaria Indicator Surveys (MISs). PLoS ONE. 2017;12: e0175537.
38. Chirombo J, Lowe R, Kazembe L. Using structured additive regression models to estimate risk factors of malaria: analysis of 2010 Malawi malaria indicator survey data. PLoS ONE. 2014;9: e101116.
39. Kabaghe AN, Chipeta MG, McCann RS, Phiri KS, van Vugt M, Takken W, et al. Adaptive geostatistical sampling enables efficient identification of malaria hotspots in repeated cross-sectional surveys in rural Malawi. PLoS ONE. 2017;12: e0172266.
40. Mangani C, Frake AN, Chipula G, Mkwaila W, Kakota T, Mambo I, et al. Proximity of residence to irrigation determines malaria risk and *Anopheles* abundance at an irrigated agroecosystem in Malawi. Am J Trop Med Hyg. 2021;106:283–92.
41. Snyman K, Mwangwa F, Bigira V, Kapisi J, Clark TD, Osterbauer B, et al. Poor housing construction associated with increased malaria incidence in a cohort of young Ugandan children. Am J Trop Med Hyg. 2015;92:1207–13.
42. Ssempiira J, Nambuusi B, Kissa J, Agaba B, Makumbi F, Kasasa S, et al. Geostatistical modelling of malaria indicator survey data to assess the effects of interventions on the geographical distribution of malaria prevalence in children less than 5 years in Uganda. PLoS ONE. 2017;12: e0174948.
43. Wanzirah H, Tusting LS, Arinaitwe E, Katureebe A, Maxwell K, Rek J, et al. Mind the gap: house structure and the risk of malaria in Uganda. PLoS ONE. 2015;10: e0117396.
44. Gari T, Kenea O, Loha E, Deressa W, Hailu A, Balkew M, et al. Malaria incidence and entomological findings in an area targeted for a cluster-randomized controlled trial to prevent malaria in Ethiopia: results from a pilot study. Malar J. 2016;15:145.
45. Haji Y, Fogarty AW, Deressa W. Prevalence and associated factors of malaria among febrile children in Ethiopia: a cross-sectional health facility-based study. Acta Trop. 2016;155:63–70.
46. de Glanville WA, Thomas LF, Cook EAJ, Bronsvoort BMDC, Wamae NC, Kariuki S, et al. Household socio-economic position and individual infectious disease risk in rural Kenya. Sci Rep. 2019;9:2972.
47. Florey LS, King CH, Van Dyke MK, Muchiri EM, Mungai PL, Zimmerman PA, et al. Partnering parasites: evidence of synergism between heavy *Schistosoma haematobium* and *Plasmodium* species infections in Kenyan children. PLoS Negl Trop Dis. 2012;6: e1723.
48. Siri JG, Wilson ML, Murray S, Rosen DH, Vulule JM, Slutsker L, et al. Significance of travel to rural areas as a risk factor for malarial anemia in an urban setting. Am J Trop Med Hyg. 2010;82:391–7.
49. Williams J, Njie F, Cairns M, Bojang K, Coulibaly SO, Kayentao K, et al. Non-falciparum malaria infections in pregnant women in West Africa. Malar J. 2016;15:53.
50. Zoungrana A, Chou YJ, Pu C. Socioeconomic and environment determinants as predictors of severe malaria in children under 5 years of age admitted in two hospitals in Koudougou district, Burkina Faso: a cross sectional study. Acta Trop. 2014;139:109–14.
51. Ma C, Claude KM, Kibendelwa ZT, Brooks H, Zheng X, Hawkes M. Is maternal education a social vaccine for childhood malaria infection? A cross-sectional study from war-torn Democratic Republic of Congo. Pathog Glob Health. 2017;111:98–106.
52. Emina JBO, Doctor HV, Yé Y. Profiling malaria infection among under-five children in the Democratic Republic of Congo. PLoS ONE. 2021;16: e0250550.
53. Mann DM, Swahn MH, McCool S. Undernutrition and malaria among under-five children: findings from the 2018 Nigeria demographic and health survey. Pathog Glob Health. 2021;115:423–33.
54. Vincenz C, Dolo Z, Saye S, Lovett JL, Strassmann BI. Risk factors for placental malaria, sulfadoxine-pyrimethamine doses, and birth outcomes in a rural to urban prospective cohort study on the Bandiagara Escarpment and Bamako, Mali. Malar J. 2022;21:110.
55. Temu EA, Coleman M, Abilio AP, Kleinschmidt I. High prevalence of malaria in Zambezia, Mozambique: the protective effect of IRS versus increased risks due to pig-keeping and house construction. PLoS ONE. 2012;7: e31409.
56. Ejigu BA. Geostatistical analysis and mapping of malaria risk in children of Mozambique. PLoS ONE. 2020;15: e0241680.
57. Sakwe N, Bigoga J, Ngondi J, Njeambosay B, Esemu L, Kouambeng C, et al. Relationship between malaria, anaemia, nutritional and socio-economic status amongst under-ten children, in the North Region of Cameroon: a cross-sectional assessment. PLoS ONE. 2019;14: e0218442.
58. Mmbando BP, Segeja MD, Msangeni HA, Sembuche SH, Ishengoma DS, Seth MD, et al. Epidemiology of malaria in an area prepared for clinical trials in Korogwe, north-eastern Tanzania. Malar J. 2009;8:165.
59. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. Psychol Methods. 2010;15:309.
60. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51:1173.
61. WHO. Global technical strategy for malaria 2016–2030. Geneva: World Health Organization; 2015.

62. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. Epidemiology. 2012;23:1–9.
63. Macintyre K, Keating J, Sosler S, Kibe L, Mbogo CM, Githeko AK, et al. Examining the determinants of mosquito-avoidance practices in two Kenyan cities. Malar J. 2002;1:14.
64. Njama D, Dorsey G, Guwatudde D, Kigonya K, Greenhouse B, Musisi S, et al. Urban malaria: primary caregivers' knowledge, attitudes, practices and predictors of malaria incidence in a cohort of Ugandan children. Trop Med Int Health. 2003;8:685–92.
65. Wafula ST, Mendoza H, Nalugya A, Musoke D, Waiswa P. Determinants of uptake of malaria preventive interventions among pregnant women in eastern Uganda. Malar J. 2021;20:5.
66. Onwujekwe O, el Malik F, Mustafa SH, Mnzavaa A. Do malaria preventive interventions reach the poor? Socioeconomic inequities in expenditure on and use of mosquito control tools in Sudan. Health Policy Plan. 2006;21:10–6.
67. Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;2:CD000363.
68. Pryce J, Medley N, Choi L. Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. Cochrane Database Syst Rev. 2022;1:CD012688.
69. Mumbengegwi DR, Sturrock H, Hsiang M, Roberts K, Kleinschmidt I, Nghipumbwa M, et al. Is there a correlation between malaria incidence and IRS coverage in western Zambezi region, Namibia? Public Health Action. 2018;8:S44–9.
70. Goesch JN, Schwarz NG, Decker ML, Oyakhirome S, Borchert LB, Kombila UD, et al. Socio-economic status is inversely related to bed net use in Gabon. Malar J. 2008;7:60.
71. VanderWeele TJ, TchetgenTchetgen EJ. Mediation analysis with time varying exposures and mediators. J R Stat Soc Ser B Stat Methodol. 2017;79:917–38.

Supplementary files

Additional file 1: Detailed search strategy, conducted on May 31st 2022.

MEDLINE (Pubmed):

"(malaria OR plasmodium OR fever) AND (socioeconomic status OR socio-economic status OR socioeconomic position OR socio-economic position OR income OR wealth OR poverty OR equity OR house* OR employment* OR occupation* OR education*) AND (mediator OR mediation OR Path*) AND (sub saharan africa OR sub-saharan africa OR ssa OR angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cabo verde OR cape verde OR central african republic OR chad OR comoros OR democratic republic of congo OR congo OR cote d'ivoire OR djibouti OR equatorial guinea OR eritrea OR eswatini OR swaziland OR ethiopia OR gabon OR the gambia OR ghana OR guinea OR guinea-bissau OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR mayotte OR mozambique OR namibia OR niger OR nigeria OR réunion OR rwanda OR sao tome and principe OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR south sudan OR sudan OR swaziland OR tanzania OR togo OR uganda OR zambia OR zimbabwe)"

Web of Science:

In Web of Science following databases were included: Web of Science, Biosis Citation Index (BCI), Current Conten Connect (CCC), Data Citation Index (DRCI), Korean Journal Databank (KJD), Medline (Pubmed), Russian Science Citation Index (RSCI), and Scielo Citation Index.

"TS=((malaria OR plasmodium OR fever) AND (socioeconomic status OR socioeconomic position OR income OR wealth OR poverty OR equity OR house* OR employment* OR occupation* OR education*) AND (mediator OR mediation OR Path*)) AND (CU= (sub Saharan africa OR sub-saharan africa OR ssa OR angola OR benin OR botswana OR burkina faso OR burundi OR cameroon OR cabo verde OR cape verde OR central african republic OR chad OR comoros OR democratic republic of congo OR congo OR cote d'ivoire OR djibouti OR equatorial guinea OR eritrea OR eswatini OR swaziland OR ethiopia OR gabon OR the gambia OR ghana OR guinea OR guinea-bissau OR kenya OR lesotho OR liberia OR madagascar OR malawi OR mali OR mauritania OR mauritius OR mayotte OR mozambique OR namibia OR niger OR nigeria OR réunion OR rwanda OR sao tome and principe OR senegal OR seychelles OR sierra leone OR somalia OR south africa OR south sudan OR sudan OR swaziland OR tanzania OR togo OR uganda OR zambia OR zimbabwe)) Databases= WOS, BCI, CCC, DRCI, KJD, MEDLINE, RSCI, SCIELO Timespan=2000-2022
Search language=English"

Additional file 2. Quality assessment tool for quantitative studies-adapted

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION STRONG 1 MODERATE 2 WEAK 3

B) STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Cohort (one group pre + post (before and after))
5 Case-control
6 Cross sectional study
7 Can't tell

Was the study described as randomized? If NO, go to Component C.

No Yes

If Yes, was the method of randomization described? (See dictionary)

No Yes

If Yes, was the method appropriate? (See dictionary)

No Yes

RATE THIS SECTION STRONG 1 MODERATE 2 WEAK 3

C) CONTROL OF CONFOUNDING

(Q1) Did the authors attempt to control for cofounders?

1 Yes
2 No
3 Can't tell

The following are examples of confounders:

1 Education
2 Income
3 Sex
4 Age
5 ITN use OR IRS use
6 Antimalaria treatment
7 Healthcare seeking behaviour

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g.stratification, matching) or analysis)?

1 80 – 100% (most)
2 60 – 79% (some)
3 Less than 60% (few or none)
4 Can't Tell

RATE THIS SECTION STRONG 1 MODERATE 2 WEAK 3

D) Exposure measurement

(Q1) Was the measurement of the exposure done in a way to minimize bias? (Check consistency and validity of method)

1 Yes
2 No,
3 No /Can't tell

RATE THIS SECTION STRONG 1 MODERATE 2 WEAK 3

E) Outcome measurement

(Q1) Was the measurement of the outcome done in a way to minimize bias? (Check consistency and validity of method)

1. Yes (objective /blinded)
2. No (self-report, not measured using reference standard)
3. Can't tell or not mentioned

For cohort, check length of follow up-long enough?

RATE THIS SECTION STRONG 1 MODERATE 2 WEAK 3

F) WITHDRAWALS AND DROP-OUTS (prospective designs)

(Q1) Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?

1 Yes
2 No
3 Can't tell
4 Not Applicable (i.e. one-time surveys or interviews)

(Q2) Indicate the percentage of participants completing the study. (If the percentage differs by groups, record thelowest).

1 80 -100%
2 60 - 79%
3 less than 60%
4 Can't tell
5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION STRONG 1 MODERATE 2 WEAK 3

GLOBAL RATING

COMPONENT RATINGS
Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	**SELECTION BIAS**	**STRONG**	**MODERATE**	**WEAK**
		1	2	*3*
B	**STUDY DESIGN**	**STRONG**	**MODERATE**	**WEAK**
		1	2	*3*
C	**CONTROL OF CONFOUNDING**	**STRONG**	**MODERATE**	**WEAK**
		1	2	*3*
D	**EXPOSURE MEASUREMENT**	**STRONG**	**MODERATE**	**WEAK**
		1	2	*3*
E	**OUTCOME MEASUREMENT**	**STRONG**	**MODERATE**	**WEAK**
		1	2	*3*
F	**WITHDRAWALS ANDDROPOUTS**	**STRONG**	**MODERATE**	**WEAK**
		1	*2*	*3*

GLOBAL RATING FOR THIS PAPER (circle one):

1 STRONG (no WEAK ratings)
2 MODERATE (one WEAK rating)
3 WEAK (two or more WEAK ratings)

With both reviewers discussing the ratings:
Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?
No Yes

If yes, indicate the reason for the discrepancy
1 Oversight
2 Differences in interpretation of criteria
3 Differences in interpretation of study
Final decision of both reviewers (circle one):
  1 STRONG
  2 MODERATE
  3 WEAK

Additional file 3. Assessment of the quality of included studies (based on adapted EPHPP tool)

Study no.	Author (Year)	Selection bias	Study design	Control of confounding	Exposure measurement	Outcome measurement	Withdrawals and drop outs	Final rating
1	Chirombo et al, 2014	2	3	3	2	2	NA	Weak
2	De Granville, 2019	1	3	2	1	1	NA	Moderate
3	Florey L, et al, 2012	3	3	3	1	1	N/A	Weak
4	Gari T, et al 2016	1	2	2	2	1	1	Strong
5	Haji et al, 2016	2	3	1	2	1	NA	Moderate
6	Kabaghe, et al 2017	1	3	3	2	2	NA	Weak
7	Kahabuka C et al, 2012	2	3	3	2	2	NA	Weak
8	Liu et al 2014	1	1	2	1	1	1	Strong
9	Ma et al; 2017	1	3	2	2	1	NA	Moderate
10	Mathanga et al 2015	1	3	2	2	1	NA	Moderate
11	Sakwe et al, 2019	2	3	1	2	1	NA	Moderate
12	Siri et al; 2010	2	2	2	2	1	NA	Strong
13	Skarbinski et al; 2011	2	3	3	1	1	NA	weak
14	Skarbinski et al; 2012	1	3	3	1	1	NA	Weak
15	Snyman, et al; 2015	3	2	2	1	1	2	Moderate
16	Somi et al.;2007	2	3	1	2	1	NA	Moderate
17	Somi et al.;2008	1	3	2	1	1	NA	Moderate
18	Ssempiira et al; 2017	1	3	1	1	2	NA	Moderate
19	Temu et al.;2012	3	3	2	2	2	NA	Weak
20	Tusting et al; 2016	2	2	2	1	1	2	Strong
21	Wanzirah et al; 2015	2	2	2	2	1	2	Strong
22	West et al.; 2013	1	3	2	1	2	NA	Moderate
23	William et al; 2016	1	3	3	2	1	NA	Weak

24	Zgambo et al; 2017	1	3	2	2	1	NA	Moderate
25	Zoungrana et al;2014	2	3	1	2	1	NA	Moderate
26	Loha et al; 2012	1	2	2	2	2	1	strong
27	Graves et al; 2009	1	3	2	2	2	NA	Moderate
28	Coleman et al; 2010	1	2	3	2	1	NA	Moderate
29	Mmbando et al; 2011	1	3	2	2	1	NA	Moderate
30	Clark et al, 2008	1	2	2	2	1	2	Strong
31	Jose Siri, 2014	1	3	2	2	1	NA	Moderate
32	Custodio et al; 2009	1	3	2	2	1	NA	Moderate
33	De Beaudrap et al; 2011	1	3	2	2	1	NA	Moderate
34	Asante et al; 2013	1	2	2	2	1	2	Strong
35	Sonko et al 2014	1	3	2	2	1	NA	Moderate
36	Vincenz et al, 2022	3	2	3	2	1	3	Weak
37	Mann D, 2021	1	3	2	1	1	NA	Moderate
38	Emina JB et al, 2021	2	3	2	1	1	NA	Moderate
39	Mwaiswelo et al, 2021	3	3	2	1	2	NA	Weak
40	Mangani et al, 2022	1	3	1	1	2	NA	Moderate
41	Ejigu, 2020	3	3	2	1	2	NA	Weak

2.2. Socioeconomic disparities in *Plasmodium falciparum* infection risk in Southern Malawi: Mediation analyses

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Socioeconomic disparities in *Plasmodium falciparum* infection risk in Southern Malawi: mediation analyses

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This study investigated the mediators of the association between socioeconomic position (SEP) and *Plasmodium falciparum (Pf)* infection in Southern region of Malawi. We utilized data from the 2014 International Center of Excellence for Malaria Research (ICEMR) surveys from Malawi in which blood samples of all individuals from selected households in Blantyre, Thyolo and Chikhwawa were tested for *Pf* parasitemia. We assessed household SEP and potential mediators – housing quality, food security, education status of household heads, and use of long-lasting Insecticide-treated nets (LLINs) and nutritional status. We conducted causal mediation analyses to assess the proportion of SEP effect that is attributed to each mediator and combination of mediators. The mediation analysis shows that during the rainy season, improved housing and educational attainment explained 39.4% and 17.0% of the SEP effect on *Pf* infection, respectively, and collectively 66.4%. In the dry season, housing, educational attainment, and LLIN usage collectively mediated 33.4% of SEP's effect with individual contributions of 15.6%, 11.2%, and 3.8%, respectively. Nutrition also played a role, particularly for children, mediating 9.2% of SEP's effect in the rainy season and 3.7% in the dry season. The study concluded that multifaceted interventions targeting housing, education, LLIN usage, and nutrition are vital to reducing socioeconomic disparities in *Pf* infection risk in the Southern region of Malawi.

Keywords Malaria, Plasmodium Falciparum, Socioeconomic position, Mediation, Counterfactual framework, Malawi

Abbreviations

CI	Confidence Interval
DAG	Directed Acyclic Graph (DAG)
DHS	Demographic and Health Surveys
ICEMR	International Center of Excellence for Malaria Research
LLINs	Long-lasting insecticide-treated nets
PC	Principal Component
PCA	Principal Component Analysis
PCR	Polymerase Chain Reaction
Pf	*Plasmodium falciparum*
PR	Prevalence Ratio
SAC	School Age Children

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SEP	Socioeconomic Position
SSA	Sub-Saharan Africa
TE	Total effect
TNIE	Total natural indirect effect
TNIE	Total natural direct effect

Malaria remains a leading public health problem in sub-Saharan Africa (SSA), accounting for over 95% of the global malaria cases and deaths[1]. In Malawi, malaria, caused by *Plasmodium falciparum (Pf)*infection, is responsible for approximately 40% of all outpatient visits and 36% of all hospital deaths[2]. The disease remains endemic in most parts of the country, with transmission occurring throughout the year although it peaks during the rainy season. The transmission also tends to increase with a decrease in altitude as lower altitudes are characterized by temperatures above 17 °C, which favour the breeding of and development of vectors and parasites[3,4]. *Pf*infection transmission is heterogeneous and may be influenced by a variety of factors including socioeconomic position, climate, ecology, vector behaviour, and use of malaria preventive interventions[5].

Socioeconomic position (SEP), one of the key determinants of *Pf infection* risk, affects both the exposure to infection and the vulnerability of individuals and communities to the disease[6]. Evidence of socioeconomic inequities in relation to malaria in SSA has been well documented[7–10], with prior research indicating higher odds of malaria among persons in low SEP compared to those in high SEP households[11,12]. For example, low SEP can also affect the living conditions that favour or limit the breeding and survival of Anopheles mosquitoes, the vectors of *Plasmodium* parasites[13,14]. Households with a lower SEP are more likely to have poorer housing quality (i.e., not fully sealed), which can increase exposure to mosquitoes. Further, greater presence of open water sources due to limited access to piped water, can increase the presence of larval habitats around their dwellings[15,16].

Understanding the dynamics of how SEP influences *Pf infection* risk is complex and includes both direct and indirect effects. Previous studies have suggested that the effect of SEP on *Pf infection* is largely indirect[17,18] and hence mediated by other proximal factors on the causal pathway, such as improved housing, educational attainment, nutrition, food security, access to health care, use of long-lasting treated nets (LLINs), and indoor residual spraying[17,19,20]. However, there is limited evidence to confirm and quantify their mediating role in the association between SEP and *Pf infection*in different settings[17,19,20]. Identifying the mediating pathways can inform more effective interventions against malaria after estimating how much of the effect can be eliminated by targeting these pathways[21,22]. At present, studies that examine the mediators of the association between SEP and *Pf infection*in SSA are limited[17,23]. The few studies that exist primarily employ traditional analytical methods. These methods often overlook the confounding factors that may affect the mediator-exposure relationship and fail to consider the collective effect of multiple mediators[7,24]. This study aims to address this gap by using a causal mediation analyses to examine how improved housing quality, educational attainment of household head, food security, nutrition and LLIN use mediate the association between SEP and *Pf infection* in the Southern region of Malawi. Our findings will provide new insights into the multifaceted pathways that link SEP and *Pf infection*, and inform more effective and equitable strategies towards achieving malaria elimination in Malawi.

Methods

Study setting

The Malawi International Center of Excellence for Malaria Research (ICEMR, U.S. N.I.H. U19AI089683) conducted cross-sectional surveys between 2010 and 2017 in Malawi - a country in southern part of Africa where malaria is endemic with seasonal variation and peaks during rainy seasons. Malaria in Malawi is mainly caused by *Plasmodium falciparum*, a parasite which is transmitted by several species of anopheles mosquitoes including *Anopheles gambiae*, *Anopheles arabiensis*, and *Anopheles funestus*[25]. The two ICEMR survey rounds in 2014 focused on three of Malawi's 28 districts: Blantyre, Chikhwawa, and Thyolo. These districts are located in the south of the country, have a total population of over 2.5 million people and cover a total area of 8,569 km[26]. The malaria transmission patterns in the three districts are quite heterogeneous. Chikhwawa is a rural low-land district, which has more intensive transmission with a previous reported *Pf infection*prevalence of 20% in the dry and 32% in the rainy season[27]. Thyolo is a rural mountainous district with largely moderate transmission and a reported prevalence of 10% in dry and 15% in rainy seasons. In contrast, Blantyre is predominantly urban and is the second largest city in the country after Lilongwe with generally low levels of transmission with prevalences of 5% in the dry season and 9% in the rainy season[25].

Study design

The study's design and sampling methodologies are elaborated upon in prior publications[27,28]. In summary, two cross-sectional surveys were conducted in 2014, corresponding with Malawi's climatic seasons: one during the rainy season (April-May) and the other in the dry season (September-October). Each survey targeted a total sample size of at least 900 households, with each district contributing 300 households.

A two-stage sampling approach was employed. Initially, 10 enumeration areas (EAs) per district were selected randomly using probability proportionate to size. In Blantyre, only EAs within the city were sampled. In Thyolo, EAs bordering Chikhwawa or those at less than 500 m above sea level were excluded. Similarly, in Chikhwawa, EAs bordering Thyolo or EA at greater than 500 m above sea level were excluded. If a randomly selected EA met the exclusion criteria, it was replaced by another randomly selected EA. Next, 30 households within each EA were selected using compact segment sampling. Each selected EA was divided into segments of approximately 30 households and one segment was randomly selected. All households within the selected segment were visited, and the household head along with all consenting household members were invited to participate in the study[27]. For the dry season survey, the research teams revisited the same 30 EAs and primarily interviewed participants from households that were initially surveyed in the rainy season. It is important to note that while the same EAs were revisited, there was no specific tracking/linking of individual households or participants between the two survey rounds. This study has followed the guidelines for reporting mediation analysis studies[29]. The reporting checklist is available as Supplementary File 1.

Data collection procedures

Detailed procedures were previously published[27]. Briefly, written informed consent for participation was obtained from the head of the household, each adult household member, and a parent/guardian for all minors. Assent was obtained from children 13–17 years old. Questionnaires based on the Malaria Indicator Survey[30] were used to collect demographic data (district, age, gender, household size, educational attainment of household head), durable assets owned, LLIN ownership and use, and information regarding food security. Housing characteristics (roof type, floor type, wall type, house eaves, and windows) were observed. Fingerpick blood samples were taken from all participants for malaria PCR testing (whole collected and dried on filter paper) and from children aged 6 months to 15 years for haemoglobin testing (Hemocue®)[31].

Measurement and variables

The ***outcome*** was a PCR-confirmed *Plasmodium falciparum (Pf)* infection (which included asymptomatic or symptomatic individuals assessed during active case detection). DNA was extracted from filter papers and subsequently subjected to real-time PCR targeted to the *Pf*lactate dehydrogenase gene as previously described[27]. Real-time PCR allows for accurate, automated and real-time detection of target material, unlike conventional PCR. This enables faster acquisition of laboratory results, hence guiding infected participants to seek timely and appropriate management[32]. A positive PCR test result was indicative of *Pf infection* (coded 1), otherwise negative (coded 0).

The ***main exposure*** was household SEP, for which we constructed a wealth index using principal component analysis (PCA) of durable assets, such as ownership of radio, television, telephone, bicycle, house, electricity, and cooking fuel (clean vs. non-biomass), any income source (yes vs. no), as well as average number of persons per room (≤ 2 vs. > 2). We did not include variables on housing construction, as housing conceptually lies on the causal pathway between SEP and *Pf infection* and may have an independent direct effect on *Pf infection*risk and was hence considered as a mediator instead[6]. In our analysis, we first examined the descriptive statistics for the variables considered for PCA to assess missingness. Given that missingness was less than 0.1%, we proceeded with a complete case analysis. We used a tetrachoric correlation structure and opted not to rotate the principal components (PCs) since the rotated and non-rotated PCs yielded comparable results. The first PC, with an eigenvalue of 4.06, accounted for 45% of the total variance and was used to derive the wealth index scores. These scores were then divided into three categories—lower, medium, and high—creating a new SEP variable. The categorization followed a 40:40:20 ratio to allow for easier interpretation of the results[33,34].

Mediators for *Pf infection* and SEP included housing quality, highest educational attainment of the household head, use of LLINs, food security, and nutrition (available only for participants aged 6 months to 15 years).

- **Housing quality** served as a mediator in the association between SEP and *Pf infection*. Specifically, housing quality was categorized into two types: modern and traditional. Modern houses were those that met at least three out of the following four criteria: finished materials for the roof, floor, walls, and closed eaves. In contrast, traditional houses met less than 3 of these criteria (0 to 2 of the conditions). In line with the definitions of the Demographic and Health Surveys (DHS)[32], finished walls refer to those made of materials, such as cement, bricks, cement blocks, covered adobe, plastered wall, stone with lime and wood planks; while rudimentary walls refer to those made of materials, such as cane, palm, bamboo or stone with mud, and plywood. Finished roofs refer to those made of materials, such as metal sheets, wood, cement and roofing shingles, while natural or rudimentary roofs are made of materials, such as thatch, stick and mud, plastic sheet, bamboo, and wood planks. Finished floors refer to those made of materials, such as parquet or polished wood, vinyl or asphalt strips, ceramic tiles, cement, and carpet, while natural or rudimentary floors are made of materials, such as earth, sand, dung, wood planks, palm, and bamboo.
- **Highest educational attainment**: The highest educational attainment of the household head was categorized as follows: 'none', 'primary', and 'secondary or higher'. These categories were coded as 0, 1, and 2, respectively.
- **Food security** was assessed based on three questions posed to the household head: In the past four weeks, how often did you or a household member (1) worry about not having enough food, (2) eat smaller meal sizes than would normally be considered enough, and (3) eat fewer meals in a day because of lack of food. The response categories to these questions were none, rarely, sometimes or often. We created a binary indicator variable in which a household was considered food secure (coded 1) if the frequency of none of the three scenarios was present, otherwise categorized as food insecure (code 0).
- **Use of long-lasting insecticide-treated nets (LLINs)**: This is a mediator at the individual level and was based on the question "whether a person (participant) slept under LLINs the previous night". Affirmative responses were coded 1, otherwise coded 0. In addition, we assessed LLIN universal coverage, which is defined as having a maximum of two people per LLIN on average in a household, but we used reported LLIN use in our mediation models[35].
- **Nutrition status**: In this study, nutritional status was assessed among children aged 6 months to 15 years, using anaemia status as a proxy marker. Haemoglobin concentrations of ≥ 11.0 g/dl for children 6–59 months, 11.5 g/dl for children 5–11 years, and ≥ 12.0 g/dl for children 12–15 years were considered indicative of being free from anaemia. Children meeting these criteria were coded as '1', and those not meeting them were coded as '0'[36]. The mediating role of nutrition status was determined only for children (6 months to 15 years). It is imperative to note that while anaemia can reflect suboptimal nutritional status, it may also arise as a conse-

quence of malaria. In areas endemic for malaria, the disease itself can precipitate anaemia through hemolysis and other pathophysiological processes. Consequently, the presence of anaemia might be a result of, rather than a precursor to, malaria infection. This consideration is crucial when interpreting the mediation analysis findings as they may not be accurate.

Covariates for this study included the age of participants (< 5 years, 5–15 years and 16 + years), geographical location (Blantyre, Chikhwawa, and Thyolo), sex (male and female), and household size as discrete variables. Missingness for outcome, mediators, and key covariates is shown in Supplementary File 2.

Statistical analysis

We used descriptive statistics to summarize the baseline characteristics of households and participants in the positive *Pf infection* and -negative groups and report p-values adjusted for multiple testing. We reported numerical data as means and standard deviations and categorical data as frequencies and percentages. We used two separate regression models to assess the association between SEP and malaria as follows: For each of the seasons (rainy and dry), we ran multivariable mixed-effects modified Poisson regression models with household as a random intercept since participants from the same household are correlated. We adjusted for age, sex, household size and geographical location, and reported prevalence ratios (PRs) and 95% confidence intervals (CIs). We subsequently conducted causal mediation analyses for the association between SEP and *Pf infection using the CMaverse package*[37]. We examined the proportion mediated by improved housing quality, LLIN use, food security, highest educational attainment of the household head and anaemia free status (only among children ≥ 6 and ≤ 15 years). A Directed Acyclic Graph (DAG) for this association is depicted in Supplementary File 3. We used regression-based approaches allowing for potential exposure-mediator interactions (where possible) to estimate the total effect (TE), total natural indirect effect (TNIE), and total natural direct effect (TNDE). The TNIE was the effect of SEP on *Pf infection* explained by its association with the mediators individually and in combination. The TNDE was the effect of SEP on *Pf infection* independent of the mediator. We estimated the proportion of the association mediated by the mediator as TNIE/ [TNDE + TNIE].

We used non-parametric bootstrapping with multiple imputation to handle any missing data for some mediators (such as LLINs use (0.1%), educational attainment of household heads (0.6%), anaemia free status among those aged between 6 months and 15 years, (2.52%) and covariates, age (0.2%) and to obtain robust PRs with 95% CIs. The counterfactual assumptions included (*i*) no unmeasured confounding of the treatment-outcome relationship (*ii*) no unmeasured confounding of mediator-outcome relationship iii) no unmeasured confounding of the treatment-mediator relationship. We assumed a temporal sequence between exposure and outcomes and also conducted sensitivity analyses to assess the robustness of estimates to unmeasured confounding and reported the mediational E-values and corresponding 95% CIs closest to null. Baron and Kenny's criteria for identifying a potential mediator are provided in Supplementary File 4. Additional analyses for mediation effects based on different age groups and seasons are provided in Supplementary File 5. All analyses were run using R software.

Ethical considerations

The study obtained ethical approval from the independent Institutional Review Boards (IRBs) of the University of Malawi College of Medicine, the University of Maryland, Baltimore, and Michigan State University. The studies were performed in accordance with relevant guidelines including the Declaration of Helsinki. Informed consent was obtained from all study participants and/or their legal guardians.

Results

Individual and household characteristics by *Pf* infection status

During the study, 3,003 individuals participated in the rainy season survey, while 3,253 took part in the dry season. The majority of participants were female (61.3% in the rainy season and 60.9% in the dry season).

The prevalence of *Plasmodium falciparum (Pf)* infection differed between seasons; it was 19.7% (95% Confidence Interval, CI: 18.4 – 21.3%) in the rainy season, which decreased to 12.9% (95% CI: 11.8 – 14.1%) in the dry season. Reports of fever within the last 48 h were 7.5% in the rainy season, dropping to 3.8% in the dry season. Notably, 80.5% of participants exhibited no symptoms during the rainy season, with a slight increase to 83.8% in the dry season. Table 1 summarizes the individual and household characteristics by *Pf* infection status across both seasons.

Association between SEP and *Pf infection*during rainy and dry seasons

We assessed the association between SEP of the households and *Pf* infection in the rainy and dry seasons. Our main findings include that there was no association between household wealth and *Pf* infection risk in the rainy season (PR = 0.83, 95% CI = 0.52–1.33) and the dry season (PR = 0.57, 95% CI = 0.32–1.03). Having secondary or higher education and better housing were protective in both seasons while LLIN use appeared to be protective in the dry season (PR = 0.52, 95% CI = 0.39–0.71) (Table 2).

Mediation analysis

Mediators on the pathway between SEP and *Pf infection* in the rainy season

In the rainy season, the single mediator analyses showed that housing quality and having secondary or higher education partially mediated 39.4% and 17.0% of the effect of SEP on *Pf infection*, respectively. The multiple mediator analyses showed that the combined effect of both mediators explained 66.4% of the effect of SEP on *Pf infection*. The mediated effects through housing were consistent across age groups (Supplementary File 5). In

Characteristic	Rainy season (April /May 2014) ($N = 3{,}003$) $N = 3{,}003$[1]	Pf infection, $N = 594$[1]	No Pf infection, $N = 2{,}409$[1]	p-value*	Dry season (Sept/Oct 2014) ($N = 3{,}253$) $N = 3{,}253$[1]	Pf infection, $N = 421$[1]	No Pf infection, $N = 2{,}832$[1]	p-value*
District				< 0.001				< 0.001
Blantyre	998 (33.2%)	85 (8.5%)	913 (91.5%)		1,050 (32.3%)	56 (5.3%)	994 (94.7%)	
Chikhwawa	1,043 (34.7%)	361 (34.6%)	682 (65.4%)		1,173 (36.1%)	261 (22.3%)	912 (77.7%)	
Thyolo	962 (32.0%)	148 (15.4%)	814 (84.6%)		1,030 (31.7%)	104 (10.1%)	926 (89.9%)	
Age of participant				< 0.001				< 0.001
16+	1,339 (44.7%)	232 (17.3%)	1,107 (82.7%)		1,379 (42.5%)	125 (9.1%)	1,254 (90.9%)	
5–15	1,106 (36.9%)	268 (24.2%)	838 (75.8%)		1,272 (39.2%)	235 (18.5%)	1,037 (81.5%)	
under 5	552 (18.4%)	94 (17.0%)	458 (83.0%)		595 (18.3%)	60 (10.1%)	535 (89.9%)	
Sex of the participant				0.326				0.011
Female	1,835 (61.2%)	353 (19.2%)	1,482 (80.8%)		1,977 (60.9%)	231 (11.7%)	1,746 (88.3%)	
Male	1,164 (38.8%)	241 (20.7%)	923 (79.3%)		1,271 (39.1%)	189 (14.9%)	1,082 (85.1%)	
Household head education attainment				< 0.001				< 0.001
None	605 (20.2%)	172 (28.4%)	433 (71.6%)		601 (18.6%)	109 (18.1%)	492 (81.9%)	
Primary	1,668 (55.8%)	332 (19.9%)	1,336 (80.1%)		1,896 (58.7%)	267 (14.1%)	1,629 (85.9%)	
Secondary or higher	715 (23.9%)	85 (11.9%)	630 (88.1%)		731 (22.6%)	41 (5.6%)	690 (94.4%)	
Household size	4.6 (1.8)	4.8 (1.6)	4.6 (1.8)	0.015	4.8 (1.7)	4.9 (1.7)	4.7 (1.7)	0.040
Fever in the last 48 h								
No	2779 (92.5%)	518 (18.6%)	2261 (81.4%)	< 0.001	3129 (96.2%)	398 (12.7%)	2731 (87.3%)	0.067
Yes	224 (7.5%)	76 (33.9%)	148 (66.1%)		124 (3.8%)	23 (18.5%)	101 (81.5%)	
Socioeconomic strata				< 0.001				< 0.001
Lower	1,223 (40.7%)	311 (25.4%)	912 (74.6%)		1,177 (36.2%)	200 (17.0%)	977 (83.0%)	
Middle	1,194 (39.8%)	218 (18.3%)	976 (81.7%)		1,455 (44.7%)	195 (13.4%)	1,260 (86.6%)	
High	586 (19.5%)	65 (11.1%)	521 (88.9%)		621 (19.1%)	26 (4.2%)	595 (95.8%)	
Housing quality				< 0.001				< 0.001
Low	1,364 (45.4%)	379 (27.8%)	985 (72.2%)		1,507 (46.3%)	274 (18.2%)	1,233 (81.8%)	
High	1,639 (54.6%)	215 (13.1%)	1,424 (86.9%)		1,746 (53.7%)	147 (8.4%)	1,599 (91.6%)	
Food security				0.015				0.391
Insecure	493 (16.4%)	118 (23.9%)	375 (76.1%)		403 (12.6%)	57 (14.1%)	346 (85.9%)	
Secure	2,509 (83.6%)	476 (19.0%)	2,033 (81.0%)		2,798 (87.4%)	353 (12.6%)	2,445 (87.4%)	
Household owns LLIN(s)				0.132				< 0.001
No	487 (16.2%)	109 (22.4%)	378 (77.6%)		877 (27.0%)	151 (17.2%)	726 (82.8%)	
Yes	2,516 (83.8%)	485 (19.3%)	2,031 (80.7%)		2,376 (73.0%)	270 (11.4%)	2,106 (88.6%)	
At most 2 persons share a LLIN				< 0.001				< 0.001
No	2,201 (73.3%)	475(21.6%)	1,726 (78.4%)		2584 (79.4%)	365 (14.1%)	2,219 (85.9%)	
Yes	802 (26.7%)	119 (14.8%)	683 (85.2%)		669 (20.6%)	56 (8.4%)	613 (91.6%)	
Slept in a LLIN the previous night				0.132				< 0.001
No	1,056 (35.2%)	225 (21.3%)	831 (78.7%)		1,863 (57.3%)	302 (16.2%)	1,561 (83.8%)	
Yes	1,947 (64.8%)	369 (19.0%)	1,578 (81.0%)		1,390 (42.7%)	119 (8.6%)	1,271 (91.4%)	
Nutrition (Anemia status)[3]				< 0.001				< 0.001
Anaemia	876 (54.5%)	237 (27.1%)	639 (72.9%)		921 (50.0%)	175 (19.0%)	746 (81.0%)	
No Anaemia	730 (45.5%)	104 (14.2%)	626 (85.8%)		920 (50.0%)	114 (12.4%)	806 (87.6%)	

Table 1. Individual and household characteristics by *pf infection* status and by season. [1]n (%); Mean (SD). [2]Pearson's Chi-squared test; Welch Two Sample t-test; *p-values corrected (Benjamini & Hochberg correction for multiple testing). [3]Assessed only among participants aged 15 years and younger. Note: 23.9% of participants had secondary or higher education in the rainy season (2.5% tertiary), compared to 22.6% in the dry season (1.2% tertiary).

the subset of participants aged 6 months to 15 years, nutrition status mediated 9.2% of the effect of SEP on *Pf infection* in the rainy season.

Although indirect effects through multiple mediators were more robust to unmeasured confounding as seen by E-values, the mediated (indirect) effects through individual mediators such as housing and educational attainment were less robust. This suggests that a relatively small confounding effect could potentially explain the observed mediated estimates through individual mediators. The E-value which assesses the impact of unmeasured confounding, has values as low as 1 and $+\propto$. Larger E-values indicate a stronger association that

Characteristic	Rainy season (N = 3,003)			Dry season (N = 3,253)		
	PR[1]	95% CI[1]	p-value*	PR[1]	95% CI[1]	p-value*
Sex of participants						
Male	—	—		—	—	
Female	0.98	0.79–1.21	0.850	0.91	0.72–1.16	0.508
Age categories						
Under 5	—	—		—	—	
5–15	1.61	1.25–2.07	< 0.001	1.84	1.35–2.51	< 0.001
16+	1.81	0.25–13.3	0.644	2.31	0.30–18.1	0.508
Socioeconomic strata						
Lower	—	—		—	—	
Middle	1.07	0.83–1.39	0.644	1.18	0.88–1.59	0.349
High	0.83	0.52–1.33	0.644	0.57	0.32–1.03	0.128
Educational attainment of household head						
None	—	—		—	—	
Primary	0.73	0.56–0.95	0.038	0.81	0.59–1.11	0.291
Secondary or higher	0.53	0.36–0.78	0.004	0.48	0.28–0.80	0.017
Household size	1.11	1.03–1.19	0.014	1.06	0.97–1.15	0.291
Food Security	0.89	0.67–1.17	0.644	0.99	0.67–1.46	0.968
Slept in a LLIN the previous night	0.93	0.74–1.16	0.644	0.52	0.39–0.71	< 0.001
Housing quality (modern housing)	0.54	0.41–0.71	< 0.001	0.69	0.51–0.93	0.035
Nutrition (Anemia status)	0.54	0.41–0.71	< 0.001	0.64	0.49–0.84	0.005

Table 2. Association between SEP and *Pf infection* during the rainy and dry seasons. [1]PR = Prevalence Ratio, CI = Confidence Interval, * Benjamini & Hochberg correction for multiple testing.

is less likely to be nullified by unmeasured confounders, while lower E-values signal vulnerability to such confounding (especially when close to 1) (Fig. 1).

Mediators on the pathway between SEP and Pf infection during the dry season

In the dry season, better housing quality, secondary school or higher education, and LLIN use partially mediated 15.6%, 11.3%, and 3.8% of the effect of SEP on *Pf infection*, respectively. Multiple mediator analyses show that these three jointly mediated 33.4% of the effect of SEP. Among children aged 15 years and younger, nutrition status mediated 3.7% of the effect of SEP on *Pf infection*.

The TNIEs from individual mediator analyses were again less robust to unmeasured confounding while that from multiple mediator analyses was moderately robust (Fig. 2).

Discussion

In this study, we examined the prevalence of *Pf* infection in the general population in Southern region of Malawi and investigated/examined the direct and indirect (mediated) effects of SEP on *Pf infection* through potential mediators- housing quality, food security, LLIN use, educational attainment of household heads and nutrition status (haemoglobin) during dry and rainy seasons. The finding revealed that 19.7% of the participants had *Pf* infection during the rainy season, while 12.9% had the *Pf* infection during the dry season, underscoring the role of seasonality in *Pf*infection transmission patterns. Although these prevalence rates are high, they are comparatively lower than 37%[38]and 35.4%[39]reported in recent studies from Malawi. However, during the rainy season, the lowland Chikhwawa district had a comparable prevalence of 34.6%. The aforementioned studies focused solely on children under five and used different sampling approaches which may explain the variation in prevalence estimates. Additionally, there is well-documented significant heterogeneity in malaria transmission rates across different regions and districts in Malawi[25].

We found that higher SEP was associated with a lower probability of having *Pf* infection. This association was partially mediated by housing quality during both rainy and dry seasons with a more pronounced effect in the rainy season. The fact that higher SEP was strongly associated with improved housing, and improved housing was protective against *Pf infection*fits Baron and Kennys' main criteria for a potential mediator[40]. Improved housing may prevent the entrance of mosquito vectors and thereby reduce the mosquito biting rate, especially at night/evenings, which in turn reduces the risk of *Pf*infection[41]. Since most transmission occurs at night[42], the dwelling can be a risky place and needs to be well constructed and screened to prevent mosquito entry. Furthermore, although our study found a protective mediated effect of SEP through housing, it is important to note the shifting vector behaviour in response to widespread LLIN use over the last few years with more biting now occurring in the evening and morning and this may render housing less effective[43].

We also found that reported LLIN use explained 3.8% of the effect of SEP on *Pf infection* in the dry season, a pattern not replicated in the rainy season. This underscores the protective effectiveness of LLINs against *Pf infection*and the influence of SEP on their usage as previously highlighted[18,44,45]. In Malawi, universal bed net coverage has not yet been achieved, because insufficient amounts of LLINs are distributed for free[46]. The absence

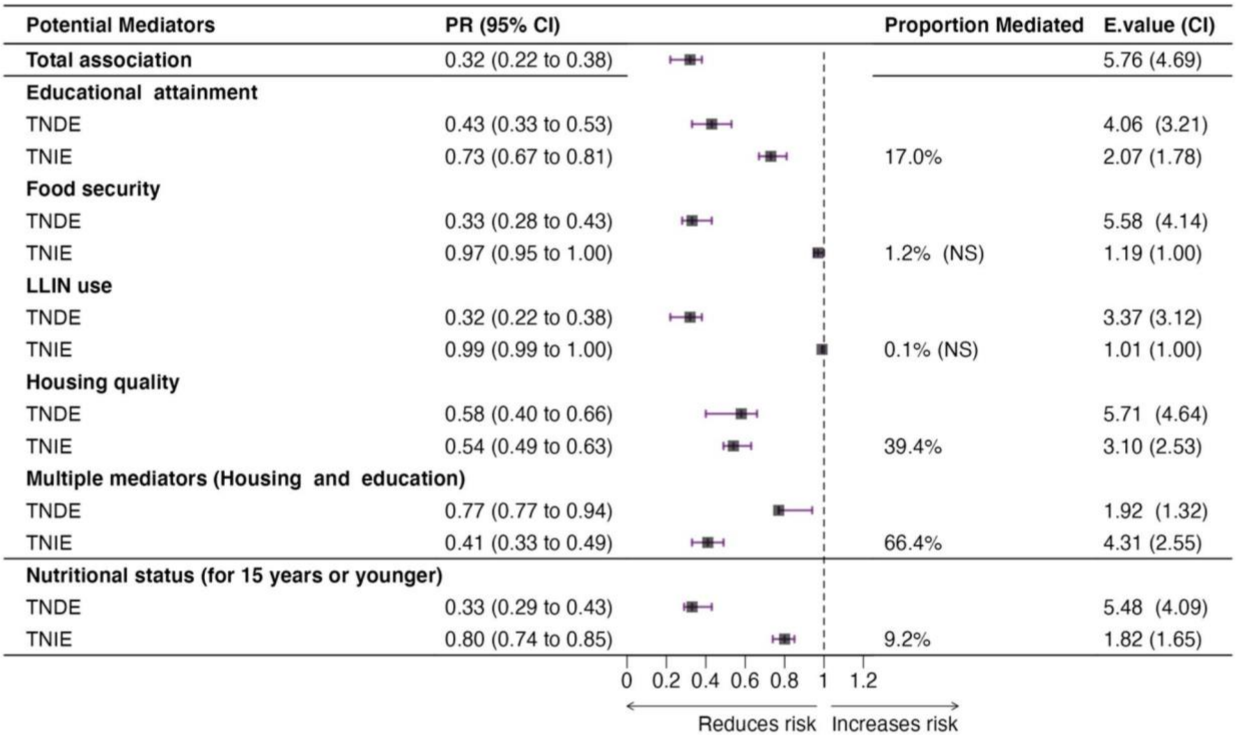

Fig. 1. Mediation analysis for the association between SEP and *Pf infection* in the rainy season. *All mediation models adjusted for age, sex and household size; multiple mediators mean a combination of mediators including potential interactions. Abbreviations: PR: Prevalence Ratio, TNDE: Total Natural Direct Effect, TNIE: Total Natural Indirect Effect. CI associated with the E-value represents the E-value of the confidence interval of the indirect effect closest to null.

of a mediated effect during the rainy season could be attributed to increased mosquito exposure during outdoor activities and a higher indoor mosquito population, which means people have a higher chance of getting bitten before they use the LLINs whilst sleeping in the evenings. This negates the protective effects of LLIN to some extent and necessitates the use of additional control measures.

Among children aged 15 years and younger, we found that improved nutritional status mediated 9.2% of the effect of SEP on the risk of *Pf infection* during the rainy season, and 3.7% during the dry season. This mediating effect was evident across both under-5 and SAC in the rainy season but was limited to SAC in the dry season. Previous research has reported mixed findings regarding the associations between nutritional status and *Pf infection*[47,48], yet there is growing consensus that malnutrition may increase susceptibility to *Pf*infection[49]. Traditional measures of nutritional status, such as stunting or wasting, have been used in these studies, but they fail to capture micronutrient deficiencies, that can occur even in children who are neither stunted nor wasted. Our study employed haemoglobin levels as a proxy for nutritional status, given its strong correlation with various indicators of malnutrition across all age groups[50]. However, it is crucial to interpret this association with caution. The cross-sectional nature presents difficulties in establishing a clear temporal sequence, especially in light of the known bidirectional relationship between anaemia and *Pf*infection especially in endemic settings such as Malawi[51]. Despite these complexities, the link between malnutrition and compromised immune function—which heightens the risk of infections such as Pf—cannot be overlooked but rather needs to be investigated in a truly longitudinal design where we can accurately determine temporarity. Nonetheless, improving nutritional status may be vital to mitigate some of the poverty-related impacts on the incidence of *Pf infection*by enhancing immune defences[49].

Education has been shown to have a positive impact on a whole range of health-related outcomes. In this study, we found that having household heads educated to tertiary level partially mediated the effect of SEP on the risk of *Pf infection* among household members. This was also confirmed in seasonal and aged-based sub-group analyses – except for adults in the dry season. We hypothesize that higher SEP enables high educational attainment and when household heads are well-educated, then they are more likely to know about and use preventive measures (Supplementary File 6), such as using LLINs, clearing breeding grounds, proactive acquisition of insect sprays, which consequently reduces exposure to mosquito vectors and hence *Pf infection*risk[52]. Moreover, higher education also comes with more financial power to procure some of these preventive measures but may also

Potential Mediators	PR (95% CI)	Proportion Mediated	E.value (CI)
Total association	0.21 (0.18 to 0.24)		8.91 (7.64)
Educational attainment			
TNDE	0.30 (0.26 to 0.39)		8.87 (5.99)
TNIE	0.70 (0.62 to 0.71)	11.3%	2.19 (2.16)
Food security			
TNDE	0.21 (0.12 to 0.31)		6.65 (4.72)
TNIE	0.99 (0.99 to 1.00)	0.01% (NS)	1.02 (1.00)
LLIN use			
TNDE	0.24 (0.20 to 0.30)		7.72 (6.19)
TNIE	0.88 (0.85 to 0.94)	3.8%	1.54 (1.34)
Housing quality			
TNDE	0.33 (0.29 to 0.39)		5.47 (4.56)
TNIE	0.63 (0.59 to 0.64)	15.6%	2.53 (2.45)
Multiple mediators (Housing, education and LLIN use)			
TNDE	0.47 (0.31 to 0.63)		3.67 (2.55)
TNIE	0.44 (0.35 to 0.48)	33.4%	3.94 (3.56)
Nutritional status (for 15 years or younger)			
TNDE	0.25 (0.15 to 0.33)		7.48 (5.42)
TNIE	0.88 (0.85 to 0.91)	3.7%	1.51 (1.43)

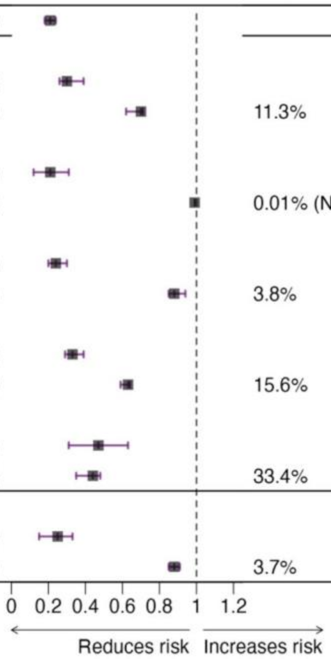

Fig. 2. Mediation analysis for the association between SEP and *Pf infection* during the dry season. *All mediation models adjusted for age, sex and household size; multiple mediators mean a combination of mediators including potential interactions. Abbreviations: PR: Prevalence Ratio, TNDE: Total Natural Direct Effect, TNIE: Total Natural Indirect Effect. CI associated with the E-value represents the E-value of the confidence interval of the indirect effect closest to null.

facilitate earlier symptom recognition and timely treatment seeking[53]. This shows that as part of the long-term efforts to eradicate malaria, improving education attainment is an important socio-structural intervention that should be promoted.

Our findings indicate that employing a combination of mediators—improved housing and education, during the rainy season, and the same factors with LLIN usage in the dry season—had a synergistic effect on reducing *Pf infection* risk. Targeting multiple mediators appears to be more effective than single-mediator strategies and findings were more robust to unmeasured confounding. Notably, the impact of these mediators is stronger during the rainy season, a period of heightened malaria transmission, underscoring their critical importance. In the rainy season, the combined effect of these mediators is particularly pronounced in adults but also children under 5 who represent the age group with the highest malaria-related mortality rates. The relatively lower indirect effect among the SAC suggests the existence of alternative pathways through which SEP influences *Pf infection*risk in this subgroup, which merits further investigation. Conversely, in the dry season, the proportion of the mediated effect of SEP is considerably lower. These may be due to decreased mosquito populations, a corresponding lower transmission rate, and possibly lower utilization of LLINs in the dry as compared to during the rainy season. Moreover, evidence shows that a higher proportion of dry season pf infections are chronic as opposed to incident, acute infections. Thus, they may be less influenced by exposure-related mediators and more related to other factors such as immunity, and age[54] These findings suggest the need for constant adaptation of preventive strategies in different seasons. Additionally, for individuals aged between 6 months to 15 years, the inclusion of better nutritional status with other mediators (housing, educational attainment and LLIN use (dry season)) further enhances the mediated protective effect against *Pf infection*, particularly in the rainy season, again highlighting the importance of season-specific intervention strategies. The results underscore the need for integrated malaria control measures that address multiple risk factors simultaneously.

This is one of the first studies to consider several socio-structural mediators of the association between SEP and *Pf infection*, individually and jointly, adding to the body of knowledge on the relationship between wealth/poverty and *Pf infection*. Our study contributes to the malaria control efforts by providing more comprehensive results from a counterfactual perspective. Our study also utilized PCR-based *Pf*test results, ensuring high sensitivity, and specificity, and the ability to detect submicroscopic malaria unlike microscopy or rapid diagnostic tests used in previous studies[55]. Limitations of this study include the inability to make causal claims due to the cross-sectional design and challenges around temporality, however, most of the exposures and mediators are structural and long-term (except for indicators of nutritional status), so we can be reasonably confident that they preceded the occurrence of *Pf* infection. Second, while the direct effect of SEP was robust to unmeasured confounding, the indirect/mediated effect through the individual mediators housing and LLIN use was less robust, which indicates that a confounding variable with a 2-fold increase in risk on a risk ratio scale would effectively sway the observed mediated effect to the null. However, this finding is still important in guiding the design of houses such as closing eaves or closing all possible entry points of mosquitoes inside the indoor spaces. Similarly, even a modest mediated effect through LLIN use suggests that improving universal LLIN coverage and use could help reduce *Pf infection* risk, highlighting the critical need to enhance distribution efforts. The third limitation is that the nature of the design violates the stringent identifiability assumptions required for causal interpretation, however, sensitivity analysis for unmeasured confounding was conducted to guide the causal interpretation. Lastly, the potential measurement errors in some of the mediators, such as food security and LLIN use (self-reporting bias) may introduce bias and affect the robustness of the findings, however, these results still provide an important source of hypotheses for future well-designed longitudinal studies.

Conclusions

Improvements in housing quality, education, LLIN coverage and nutritional status have been highlighted as mediators and these warrant further investigation of their role in the association between poverty and *Pf infection* in longitudinal designs and settings. More potential mediators should be assessed to understand the complex pathways between poverty and *Pf infection* in different settings to be able to guide appropriate targeted structural interventions that can ensure sustained malaria control.

Data availability

Data are available upon request from corresponding author because the database contains personal identifiers. Any requests for the data will be reviewed by the relevant institutional review boards.

Received: 2 May 2024; Accepted: 31 October 2024
Published online: 08 November 2024

References

1. World malaria report: 20 years of global progress and challenges (2020). https://apps.who.int/iris/rest/bitstreams/1321872/retrieve.
2. National Malaria Control Programme. *Malaria Strategic Plan 2011–2015: Towards Universal Access. In. Lilongwe* (Government of Malawi, Ministry of Health, 2010).
3. Bødker, R. et al. Relationship between altitude and intensity of malaria transmission in the Usambara Mountains, Tanzania. *J. Med. Entomol.* **40**(5), 706–717 (2003).
4. Tuno, N., Farjana, T., Uchida, Y., Iyori, M. & Yoshida, S. Effects of temperature and nutrition during the larval period on life history traits in an invasive malaria vector anopheles stephensi. *Insects* **14**(6), 543 (2023).
5. Castro, M. C. Malaria transmission and prospects for malaria eradication: The role of the environment. *Cold Spring Harb Perspect. Med.* **7**(10), a025601 (2017).
6. Degarege, A., Fennie, K., Degarege, D., Chennupati, S. & Madhivanan, P. Improving socioeconomic status may reduce the burden of malaria in sub Saharan Africa: A systematic review and meta-analysis. *PloS One*. **14**(1), e0211205 (2019).
7. Natama, H. M. et al. Malaria incidence and prevalence during the first year of life in Nanoro, Burkina Faso: A birth-cohort study. *Malar. J.* **17**(1), 163 (2018).
8. Roberts, D. & Matthews, G. Risk factors of malaria in children under the age of five years old in Uganda. *Malar. J.* **15**, 246–246 (2016).
9. Zgambo, M., Mbakaya, B. C. & Kalembo, F. W. Prevalence and factors associated with malaria parasitaemia in children under the age of five years in Malawi: A comparison study of the 2012 and 2014 Malaria Indicator surveys (MISs). *PloS One* **12**(4), e0175537 (2017).
10. Nyarko, S. H. & Cobblah, A. Sociodemographic determinants of Malaria among under-five children in Ghana. *Malar. Res. Treat.* **2014**, 304361–304361 (2014).
11. Tusting, L. S. et al. Socioeconomic development as an intervention against malaria: A systematic review and meta-analysis. *Lancet* **382**(9896), 963–972 (2013).
12. Krefis, A. C. et al. Principal component analysis of socioeconomic factors and their association with malaria in children from the Ashanti Region, Ghana. *Malar. J.* **9**, 201–201 (2010).
13. Dowling, Z., Ladeau, S. L., Armbruster, P., Biehler, D. & Leisnham, P. T. Socioeconomic status affects mosquito (diptera: culicidae) larval habitat type availability and infestation level. *J. Med. Entomol.* **50**(4), 764–772 (2013).
14. Liu, J. X. et al. Is housing quality associated with malaria incidence among young children and mosquito vector numbers? Evidence from Korogwe, Tanzania. *PLoS One* **9**(2), e87358 (2014).
15. Swope, C. B. & Hernández, D. Housing as a determinant of health equity: A conceptual model. *Soc. Sci. Med.* **243**, 112571 (2019).
16. Sedai, A. K. Who benefits from piped water in the house? Empirical evidence from a gendered analysis in India. In: *ADBI Working Paper Series* (Asian Development Bank Institute, 2021).
17. Tusting, L. S. et al. Why is malaria associated with poverty? Findings from a cohort study in rural Uganda. *Infect. Dis. Poverty.* **5**(1), 78 (2016).
18. Wafula, S. T. et al. What are the pathways between poverty and malaria in sub-saharan Africa? A systematic review of mediation studies. *Infect. Dis. Poverty* **12**(1), 58 (2023).
19. Fobil, J. N., Kraemer, A., Meyer, C. G. & May, J. Neighborhood urban environmental quality conditions are likely to drive malaria and diarrhea mortality in Accra, Ghana. *J. Environ. Public. Health* **2011**, 484010 (2011).
20. Barat, L. M. et al. Do malaria control interventions reach the poor? A view through the equity lens. *Am. J. Trop. Med. Hyg.* **71**(2 Suppl), 174–178 (2004).
21. Sagara, I., Giorgi, R., Doumbo, O. K., Piarroux, R. & Gaudart, J. Modelling recurrent events: Comparison of statistical models with continuous and discontinuous risk intervals on recurrent malaria episodes data. *Malar. J.* **13**, 293–293 (2014).
22. Twisk, J. W. R., Smidt, N. & de Vente, W. Applied analysis of recurrent events: A practical overview. *J. Epidemiol. Community Health*. **59**(8), 706–710 (2005).
23. de Glanville, W. A. et al. Household socio-economic position and individual infectious disease risk in rural Kenya. *Sci. Rep.* **9**(1), 2972 (2019).

24. Le Port, A. et al. Infections in infants during the first 12 months of life: Role of placental malaria and environmental factors. *PloS One* **6**(11), e27516–e27516 (2011).
25. Mathanga, D. P. et al. Malaria control in Malawi: Current status and directions for the future. *Acta Trop.* **121**(3), 212–217 (2012).
26. National Statistical Office. *2018 Malawi Population and Housing Census: Preliminary Report* (National Statistical Office, 2018).
27. Walldorf, J. A. et al. School-age children are a reservoir of malaria infection in Malawi. *PLOS ONE* **10**(7), e0134061 (2015).
28. Cohee, L. M. et al. Understanding the intransigence of malaria in Malawi. *Am. J. Trop. Med. Hyg.* **107**(4_Suppl), 40–48 (2022).
29. Lee, H. et al. A Guideline for reporting mediation analyses of randomized trials and observational studies: The AGReMA statement. *JAMA* **326**(11), 1045–1056 (2021).
30. WHO. Malaria indicator survey: Basic documentation for survey design and implementation. In (2005).
31. Nkrumah, B. et al. Hemoglobin estimation by the HemoCue® portable hemoglobin photometer in a resource poor setting. *BMC Clin. Pathol.* **11**, 1–6 (2011).
32. Gadalla, A. A. et al. Associations between season and gametocyte dynamics in chronic plasmodium falciparum infections. *PLoS One*. **11**(11), e0166699 (2016).
33. Filmer, D. & Pritchett, L. H. Estimating wealth effects without expenditure data–or tears: An application to educational enrollments in states of India. *Demography* **38**(1), 115–132 (2001).
34. Vyas, S. & Kumaranayake, L. Constructing socio-economic status indices: How to use principal components analysis. *Health Policy Plann.* **21**(6), 459–468 (2006).
35. MEASURE Evaluation, DHS MEASURE, President's Malaria Initiative, Roll Back Malaria Partnership, UNICEF, WHO: Household survey indicators for malaria control. In (2013).
36. WHO. *Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Vitamin and Mineral Nutrition Information System* (World Health Organization, 2011).
37. Shi, B., Choirat, C., Coull, B. A., VanderWeele, T. J. & Valeri, L. CMAverse: A suite of functions for reproducible causal mediation analyses. *Epidemiology* **32**(5), e20–e22 (2021).
38. Gaston, R. T. & Ramroop, S. Prevalence of and factors associated with malaria in children under five years of age in Malawi, using malaria indicator survey data. *Heliyon* **6**(5), e03946 (2020).
39. Chilanga, E., Collin-Vézina, D., MacIntosh, H., Mitchell, C. & Cherney, K. Prevalence and determinants of malaria infection among children of local farmers in Central Malawi. *Malar. J.* **19**(1), 308 (2020).
40. Baron, R. M. & Kenny, D. A. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J. Pers. Soc. Psychol.* **51**(6), 1173 (1986).
41. Tusting, L. S. et al. The evidence for improving housing to reduce malaria: A systematic review and meta-analysis. *Malar. J.* **14**, 209 (2015).
42. Huho, B. et al. Consistently high estimates for the proportion of human exposure to malaria vector populations occurring indoors in rural Africa. *Int. J. Epidemiol.* **42**(1), 235–247 (2013).
43. Monroe, A. et al. Methods and indicators for measuring patterns of human exposure to malaria vectors. *Malar. J.* **19**(1), 207 (2020).
44. Wafula, S. T., Mendoza, H., Nalugya, A., Musoke, D. & Waiswa, P. Determinants of uptake of malaria preventive interventions among pregnant women in eastern Uganda. *Malar. J.* **20**(1), 5–5 (2021).
45. Kooko, R., Wafula, S. T. & Orishaba, P. Socioeconomic determinants of malaria prevalence among under five children in Uganda: Evidence from 2018-19 Uganda Malaria Indicator Survey. *J. Vector Borne Dis.* **60**(1), 38–48 (2023).
46. Chanda, E. et al. Scale-up of integrated malaria vector control: Lessons from Malawi. *Bull. World Health Organ.* **94**(6), 475–480 (2016).
47. Sazawal, S. et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: Community-based, randomised, placebo-controlled trial. *Lancet* **367**(9505), 133–143 (2006).
48. Das, D. et al. Complex interactions between malaria and malnutrition: A systematic literature review. *BMC Med.* **16**(1), 186 (2018).
49. Caulfield, L. E., Richard, S. A. & Black, R. E. Undernutrition as an underlying cause of malaria morbidity and mortality in children less than five years old. *The Intolerable Burden of Malaria II: What's New, What's Needed: Supplement to Volume 71 (2) of the American Journal of Tropical Medicine and Hygiene* (2004).
50. Mitrache, C. et al. Anemia: An indicator for malnutrition in the elderly. *Ann. Hematol.* **80**(5), 295–298 (2001).
51. Kateera, F. et al. Malaria, anaemia and under-nutrition: Three frequently co-existing conditions among preschool children in rural Rwanda. *Malar. J.* **14**(1), 440 (2015).
52. Emina, J. B. O., Doctor, H. V. & Yé, Y. Profiling malaria infection among under-five children in the Democratic Republic of Congo. *PloS One* **16**(5), e0250550 (2021).
53. Wanzira, H. et al. Factors associated with malaria parasitaemia among children under 5 years in Uganda: A secondary data analysis of the 2014 Malaria Indicator Survey dataset. *Malar. J.* **16**(1), 191–191 (2017).
54. Stadler, E. et al. Evidence for exposure dependent carriage of malaria parasites across the dry season: Modelling analysis of longitudinal data. *Malar. J.* **22**(1), 42 (2023).
55. Berzosa, P. et al. Comparison of three diagnostic methods (microscopy, RDT, and PCR) for the detection of malaria parasites in representative samples from Equatorial Guinea. *Malar. J.* **17**(1), 333 (2018).

Acknowledgements
We extend sincere thanks to the individuals who took part in the study, the study team members responsible for data collection, the administrative and data teams at the Malaria Alert Centre, the health surveillance assistants, and the volunteers from the community. Our gratitude is also directed towards our partners, including the Malawi Ministry of Health & District Health Offices, the Malawi National Malaria Control Program, and the academic institutions involved: the Department of Biochemistry and the Malaria Alert Centre at the University of Malawi College of Medicine, along with the University of Maryland School of Medicine, and Michigan State University, for their essential collaboration.

Author contributions
STW, LMC and EL conceived the study. DPM and LMC led the primary data collection for the study. STW curated and analyzed the data. EL reviewed the analysis. EL and DIP reviewed the concept. STW wrote the initial draft and led the writing of the manuscript. EL, DIP, JM, LMC, OMA, NSS, and DPM critically reviewed the draft. All authors have read and approved the final version of the manuscript.

Funding
This work was supported by the U.S. National Institutes of Health, Bethesda, Maryland (grant number U19AI089683) for the Malawi International Center for Excellence in Malaria. Open Access funding enabled and

organized by Projekt DEAL.

Declarations

Ethics approval and consent to participate
The study obtained ethical approval from the independent Institutional Review Boards (IRBs) of the University of Malawi College of Medicine, the University of Maryland, Baltimore, and Michigan State University. The studies were performed in accordance with relevant guidelines including the Declaration of Helsinki. Informed consent was obtained from all study participants and/or their legal guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-78512-1.

Correspondence and requests for materials should be addressed to S.T.W.

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Supplementary files

Supplementary File 1- AGREMA checklist

Additional file 1: AGReMA checklist

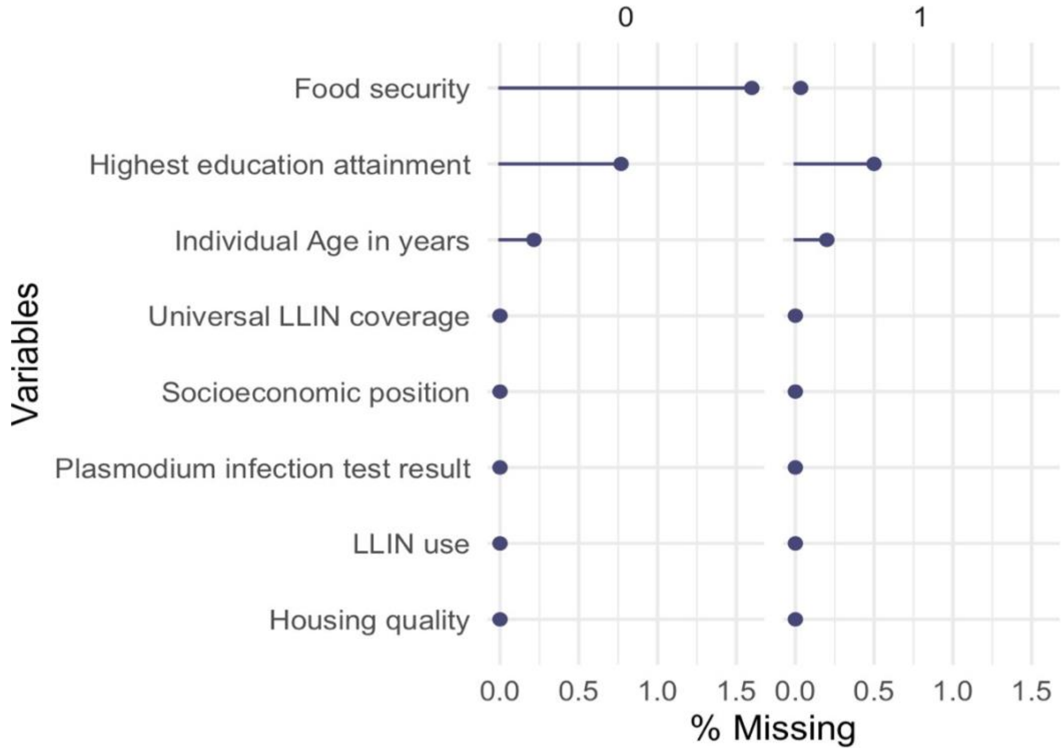
Section/Topic	Item Number	Item Description	Reported on page No
Title and abstract			
Title	1	Identify that the study uses mediation analysis	0 (cover pg)
Abstract	2	Provide a structured summary of the objectives, methods, results, and conclusions specific to mediation analyses	1
Introduction			
Background and rationale	3	Describe the study background and theoretical rationale for investigating the mechanisms of interest. Include supporting evidence or theoretical rationale for why the intervention or exposure might have a causal relationship with the proposed mediators. Include supporting evidence or theoretical rationale for why the mediators might have a causal relationship with the outcomes	4,5
Objectives	4	State the objectives of the study specific to the mechanisms of interest. The objectives should specify whether the study aims to test or estimate the mechanistic effects	5
Methods			
Study registration	5	If applicable, provide references to any protocols or study registrations specific to the mediation analysis, and highlight any deviations from the planned protocol	n/a
Study design and source of data	6	Specify the design of the original study that was used in mediation analyses and where the details can be accessed, supported by a reference. If applicable, describe study design features that are relevant to mediation analyses	5
Participants	7	Describe the target population, eligibility criteria specific to mediation analyses, study locations, and study dates (start of participant enrolment and end of follow-up)	5,6
Sample Size	8	State whether a sample size calculation was conducted for mediation analyses. If so, explain how it was calculated	N/A
Effects of interest	9	Specify the effects of interest	9
Assumed causal model	10	Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders	25
Causal assumptions	11	Specify assumptions about the causal model	9
Measurement	12	Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses. Specify how and when they were measured, the measurement properties, and whether blinded assessment was used	6 -8

Measurement levels	13	If relevant, describe the levels at which the exposure, mediator, and outcome were measured	6 -8
Statistical methods	14	Describe the statistical methods used to estimate the causal relationships of interest. This description should specify analytical strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modelling assumptions, and methods used to handle missing data. Provide a reference to the statistical software and package used	8,9
Sensitivity analyses	15	Describe any sensitivity analyses that were used to explore causal or statistical assumptions and the influence of missing data	8,9
Ethical approval	16	Name the institutional research board or ethics committee that approved the study. Provide a description of participant informed consent or ethics committee waiver of informed consent	9
Results			
Participants	17	Describe baseline characteristics of participants included in mediation analyses. Report the total sample size and number of participants lost during follow-up or with missing data	10-12
Outcomes and estimates	18	Report point estimates and uncertainty estimates for the exposure-mediator and mediator-outcome relationships. If inference concerning the causal relationship of interest is considered feasible given the causal assumptions, report the point estimate and uncertainty estimate	26, 27
Sensitivity parameters	19	Report the results from any sensitivity analyses used to assess robustness of the causal or statistical assumptions, and the influence of missing data	28,29
Discussion			
Limitations	20	Discuss the limitations of the study including potential sources of bias	18,19
Interpretation	21	Interpret the estimated effects considering the study's magnitude and uncertainty, plausibility of the causal assumptions, limitations, generalizability of the findings, and results from relevant studies	16 -18
Implications	22	Discuss the implications of the overall results for clinical practice, policy, and science	16 - 18
Other information			
Funding and role of sponsor	23	List all sources of funding or sponsorship for the mediation analysis and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit for publication.	20
Conflicts of interest and financial disclosures	24	State any conflicts of interest and financial disclosures for all authors	20
Data and code	25	Authors are encouraged to provide a statement for sharing data and code for the mediation analysis	19

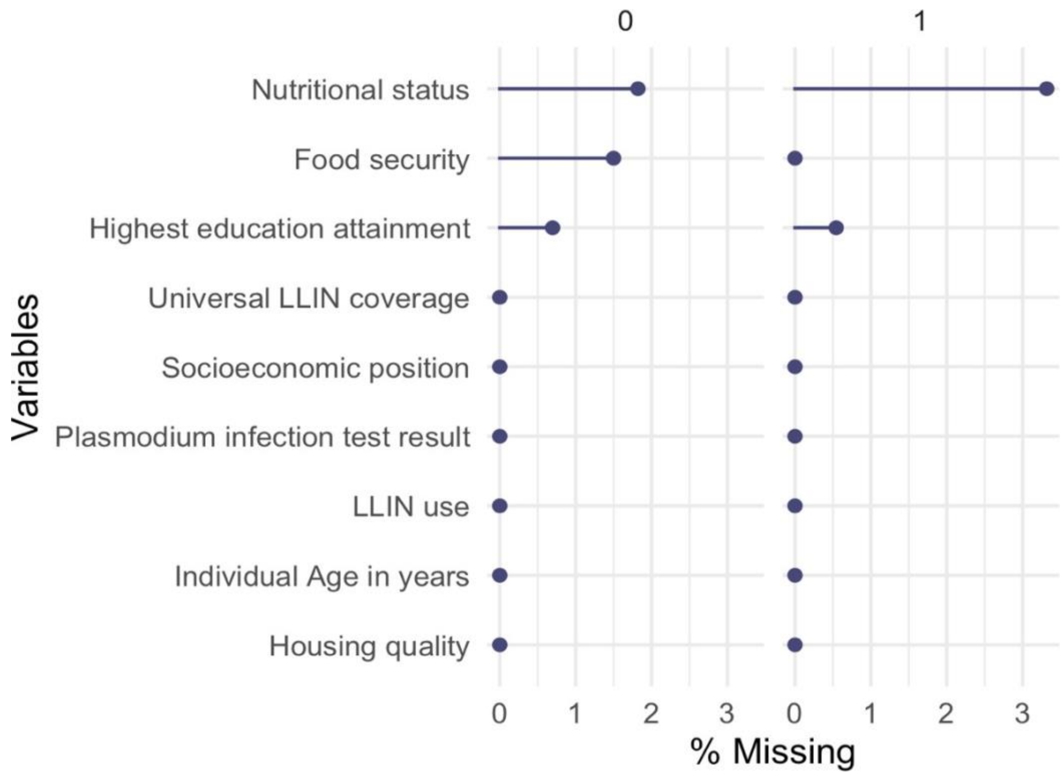
Supplementary File 2: Missingness on key variables

Additional file 2: Missingness on key variables

Overall: During dry (0) and rainy seasons (1) for all participants



Among participants aged between 6 months to 15 years



Note: Based on the findings, missingness was very low (highest being approximately 3%); no definite missing pattern and appears to be missing at random (MAR), hence multiple imputation was considered appropriate in models

Supplementary File 3- Directed acyclic graphs (DAG) for the study

DAG for the association between SEP and *P. falciparum infection*

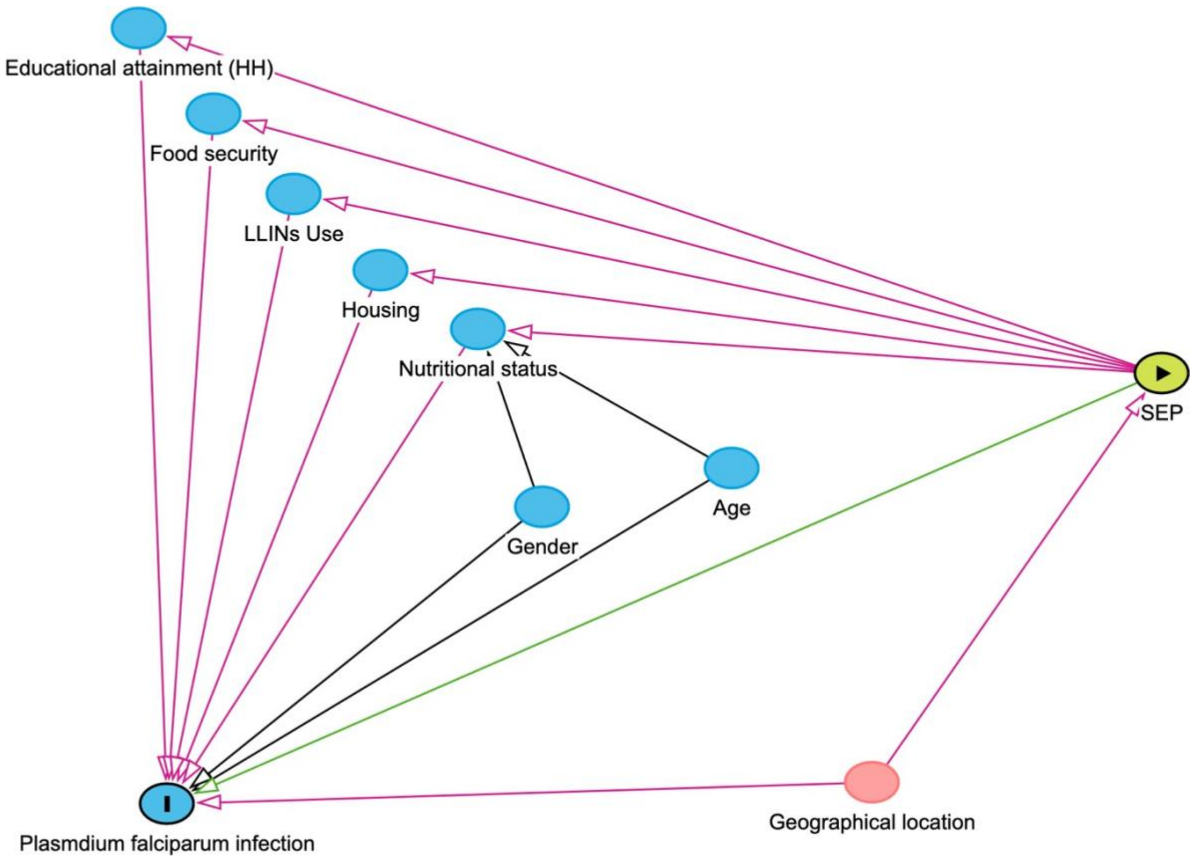
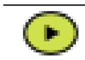


Figure 1. DAG for the association between SEP and P. falciparum infection

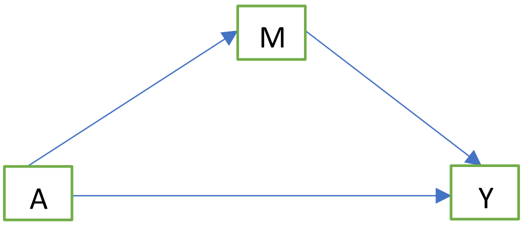
Legend / notes:

	*Exposure: Household SEP (SEP)*
	*Outcome: Plasmodium falciparum infection*
Mediators:	
	• *Nutritional status,* • *Food security,* • *Housing quality,* • *LLIN use,* • *Education attainment*
Covariates:	
	• *Location* • *Age,* • *Gender*

Supplementary File 4. Criteria for identifying mediator (The Baron and Kenny Approach, 1986)

Additional file 4. Criteria for identifying mediator (The Baron and Kenny Approach, 1986)

The causal diagram in Figure 2.1 captures the conceptualization of the role of a mediator variable. In this simple diagram, A represents an exposure variable, M denotes the mediating factor (mediator) and the outcome is denoted by Y.



Baron and Kenny suggested four criteria for identifying a mediator but only two are generally accepted as correct

1. **A change in levels of the exposure variable significantly affects the changes in the mediator (i.e., Path *from A to M)***

In our study, SEP (change from poorer to richer) should affect changes in the mediator, the unadjusted estimates for the effect of SEP on mediators is shown below

Table 1a. Unadjusted associations between SEP and the mediators

	Rainy season (N = 3,003)		**Dry season (N = 3,253)**	
Mediators	Prevalence Ratio (PR), 95% Confidence interval (CI)	p-value[2]	Prevalence Ratio (PR), 95% Confidence interval (CI)	p-value[2]
Housing quality (1=High, 0 = low)	3.61 (3.45 – 4.13)	<0.001	3.49 (3.05 – 4.00)	<0.001
Food security (1= More secure, 0= less secure)	1.18 (1.06 – 1.31)	0.002	1.16 (1.04 – 1.28)	0.006
LLIN coverage (≤2 persons per net)	1.88 (1.57 – 2.25)	<0.001	3.47 (2.83 – 4.27)	<0.001
LLIN use (sleeping under treated net previous night)	1.10 (0.97 – 1.24)	0.145	1.91 (1.66 – 2.20)	< 0.001
Educational attainment (Post primary, primary, None)	17.4 (13.9 – 21.8)	<0.001	17.3 (13.9 – 21.6)	< 0.001
Nutritional status[1] (1= No Anaemia, 0 =Anaemia)	1.92 (1.59 – 2.32)	< 0.001	1.43 (1.20 – 1.71)	<0.001

1 Assessed among 6 months to 15-year-olds (Rainy season; N = 1606, dry season; N =1,841), [2]p-values are corrected for multiple testing (Benjamin-Hochberg); In actual mediation analysis, we used LLIN use and not LLIN coverage.

2. **There is a significant relationship between the mediator and the outcome (i.e., Path from M to Y)**
   We assessed crude associations between mediators and the outcome and presented the prevalence ratios and 95%CIs

Table 1b. Unadjusted associations between each mediator and *P. falciparum infection*

	Rainy season (N = 3,003)		Dry season (N = 3,253)	
Mediators	Prevalence Ratio (PR), 95% Confidence interval (CI)	p-value	Prevalence Ratio (PR), 95% Confidence interval (CI)	p-value
Housing quality (1=High, 0 = low)	0.47 (0.40 – 0.56)	<0.001	0.46 (0.38 – 0.56)	<0.001
Food security (1= More secure, 0= less secure)	0.79 (0.65 – 0.97)	0.024	0.89 (0.68 – 1.19)	0.423
LLIN coverage (≤2 persons per net)	0.69 (0.56 – 0.85)	< 0.001	0.59 (0.44 – 0.78)	< 0.001
LLIN use (sleeping under treated net previous night)	0.89 (0.75 – 1.05)	0.166)	0.53 (0.43 – 0.65)	<0.001
Educational attainment (Post primary, primary, None)	0.85 (0.81 – 0.88)	<0.001	0.88 (0.85 – 0.91)	<0.001
Nutritional status[1] (1= No Anaemia, 0 =Anaemia)	0.53 (0.42 – 0.66)[1]	< 0.001	0.65 (0.51 – 0.82)[1]	<0.001

2 Assessed among 6 months to 15-year-olds (Rainy season; N = 1606, dry season; N =1,841); In actual mediation analysis, we used LLIN use and not LLIN coverage.

3. Third criteria are that change in levels of exposure significantly changes the outcome. This has been critiqued by many scholars including Mackinnon 2008. Consensus has now been reached that the relationship between A and Y need not be statistically significant for M to be a mediator. Lack of significant association between X and Y could be due to suppression. Suppression happens when a mediating effect of a competing process has the opposite sign of mediating effect of interest

4. When the previously defined paths are controlled, a previously significant relation between the exposure and outcome is no longer significant, with the strongest demonstration of mediation occurring when the path from the independent variable to the outcome variable is zero. This is no longer correct because there is possible partial mediation (i.e., there are potentially other mediators not considered). In any case, the change from significant to non-significant after adjusting for mediator may be just a trivial change for example p-value change from 0.049 to 0.051. Whether this small change is indicative of mediation is questionable.

- *Based on this approach; Housing, educational attainment and nutritional (both seasons), and LLIN use (dry season) would be considered strong mediator candidates.*

- *This approach has fundamental flaws and we only use it as explorative analysis. For mediation, we used modern methods – counterfactual approach to mediation which we applied in this study.*

Supplementary File 5. Mediation analysis results by different subgroups in different seasons

Table 5a: Total Effect (TE), Total Natural Direct Effect (TNDE), and Total Natural Indirect Effect (TNIE) on the association between SEP and *P. falciparum infection*, with a breakdown of proportions mediated by different pathways (Rainy season)

	6 months to 5 years (N= 552)		5-15 years (N= 1,106)		Adults, 16+ (N= 1,339)	
Mediators	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]	Estimate (95% CI)	E. Values for unmeasured confounding (confounding, RR [CI]	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]
Housing quality						
Total effect (of SEP)	0.22 (0.09 – 0.43)	8.57 [4.04]	0.26 (0.20 – 0.34)	7.21 [5.30]	0.43 (0.35 – 0.59)	4.05 [2.76]
TNDE	0.49 (0.19 – 0.88)	3.54 [1.52]	0.49 (0.31 – 0.84)	3.48 [1.69]	0.72 (0.64 – 0.88)	2.12[1.51]
TNIE	0.44 (0.40 – 0.50)	3.90 [3.41]	0.68 (0.55 – 0.77)	3.28 [2.46]	0.60 (0.51– 0.69)	2.72 [2.27]
Proportion mediated	34.8%		32.5%		51.0%	
Highest educational attainment (post primary)						
TNDE	0.37 (0.12 – 0.69)	4.85 [2.28]	0.36 (0.31 – 0.49)	5.00]3.50]	0.54(0.53 – 0.76)	3.12 [1.98]
TNIE	0.61 (0.55 – 0.71)	2.68 [2.16]	0.71 (0.65 – 0.86)	2.19 [1.59]	0.80 (0.73 – 0.84)	1.81 [1.66]
Proportion mediated	18.7%		14.3%		19.0%	
Food security (secure)						
TNDE	0.24 (0.10 – 0.44)	7.64 [3.88]	0.26 (0.21 – 0.37)	7.03 [4.84]	0.43 (0.35 – 0.51)	4.05 [3.34]
TNIE	0.92 (0.88 – 1.02)	1.41 [1.00]	0.98 (0.93 – 0.99)	1.18 [1.08]	0.99 (0.99 – 1.01)	1.02 [1.00]
Proportion mediated	2.6%		1.0%		0.0%	
LLIN use						
TNDE	0.23 (0.09 – 0.45)	8.32 [3.89]	0.25 (0.21 – 0.35)	7.21 (5.22)	0.43 (0.35 – 0.60)	4.03 [2.74]
TNIE	0.99 (0.99 – 1.03)	1.06 [1.00]	1.00 (0.99 – 1.01)	1.05 (1.00)	0.99 (0.98 – 0.99)	1.11 [1.02]
Proportion mediated	0.1%		-0.01%		0.1%	
Nutritional status (No anemia)						
TNDE	0.25 (0.09 – 0.49)	7.32 [3.52]	0.34 (0.18 – 0.39)	5.33 [4.57]		
TNIE	0.91 (0.88 – 0.97)	1.43 [1.20]	0.75 (0.70 – 0.79)	2.00 [1. 84]		
Proportion mediated	3.0%		11.6%			
Combined significant mediators						
TNDE	0.90 (0.73 – 1.76)	1.45 [1.00]	0.77 (0.67 – 1.19)	1.91 [1.00]	0.88 (0.51 – 1.17)	1.51 [1.00]
TNIE	0.25 (0.18 – 0.35)	7.34 (5.09]	0.33 (0.29 – 0.43)	5.51 [4.78]	0.49 (0.38 – 0.58)	3.51 [2.88]
Proportion mediated	87.9%		70.3%		80.0% *	

*Exposure mediator interactions present and considered.

Interpretation: *The indirect/mediated' effects (through housing, education and LLIN use) are consistently significant across the different age groups. However, the proportion mediated varies considerably with large effects among adults followed by under 5 and smaller effects among the school-age children. Good nutritional status was an important mediator for under 5 and school age children (5 – 15 years). Mediated effect through nutritional status needs to be interpreted cautiously in light of bidirectional relationship between malaria and anemia that can't be distinguished due to design limitations.*

Table 5b: Total Effect (TE), Total Natural Direct Effect (TNDE), and Total Natural Indirect Effect (TNIE) on the association between SEP and *P. falciparum infection*, with a breakdown of proportions mediated by different pathways (Dry season).

	6 months to 5 years (N= 595)		5-15 years (N= 1,272)		Adults, 16+ (N= 1,379)	
Mediators	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]
Housing quality						
Total effect	0.22 (0.20 – 0.32)	8.56 [5.70]	0.21 (0.13 – 0.24)	9.04 [7.61]	0.21 (0.08 – 0.27)	8.99 [6.89]
TNDE	0.34 (0.34 – 0.61)	5.33 [2.66]	0.34 (0.17 – 0.42)	5.31 [4.14]	0.31 (0.13 – 0.44)	5.90 [3.97]
TNIE	0.64 (0.48 – 0.69)	2.50 [2.25]	0.61 (0.54 – 0.75)	2.68 [1.98]	0.66 (0.59 – 0.69)	2.39 [2.26]
Proportion mediated	15.5%		17.1%		13.6%	
Highest educational attainment (post primary)						
TNDE	0.42 (0.30 – 0.73)	4.21 [2.07]	0.32 (0.16 – 0.46)	5.79 [3.81]	0.23 (0.15 – 0.37)	8.12 [4.80]
TNIE	0.54 (0.39 – 0.64)	3.13 [2.50]	0.66 (0.59 – 0.77)	2.38 [1.92]	0.93 (0.87 – 1.02)	1.37 [1.00]
Proportion mediated	24.8%		13.3%		2.2%	
Food security (secure)						
TNDE	0.21 (0.14 – 0.35]	9.08 [5.11]	0.21 (0.11 – 0.27)	8.87 [6.63]	0.20 (0.09 – 0.29)	9.47 [6.35]
TNIE	1.03 [0.99 – 1.04}	1.24 [1.00]	0.98 (0.90 – 1.01)	1.16 [1.00]	1.02 (0.96 – 1.08)	1.16 [1.00]
Proportion mediated	-0.2		0.0%		-0.1%	

	6 months to 5 years (N= 595)		5-15 years (N= 1,272)		Adults, 16+ (N= 1,379)	
Mediators	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]	Estimate (95% CI)	E. Values for unmeasured confounding, RR [CI]
LLIN use						
TNDE	0.25 (0.14 – 0.36)	7.46 [4.70]	0.26 (0.17 – 0.29)	7.09 [6.29]	0.21 (0.08 – 0.25)	9.22 [7.49]
TNIE	0.83 (0.83 – 0.96]	1. 70 [1.25]	0.80 (0.76 – 0.86)	1.80 [1.58]	1.02 (0.97 – 1.10)	1.17 [1.00]
Proportion mediated	5.4%		6.5%		-0.1%	
Nutritional status (No anemia)						
TNDE	0.22(0.16 – 0.26)	8.40 [5.00]	0.25 (0.13 – 0.31)	7.60 [5.86]		
TNIE	0.96 (0.94 – 1.01)	1.24 [1.00]	0.85 (0.83 – 0.90)	1.62 [1.47]		
Proportion mediated	1.1%		4.6%			
Combined mediators						
TNDE	0.60 (0.16 – 0.89)	2.71 [1.47]	0.58 (0.33– 0.78)	2.87 [1.88]	0.31 (0.13 – 0.44)	5.90 [3.97]
TNIE	0.36(0.31 – 0.51)	5.01 [3.31]	0.35 (0.31 – 0.45)	5.21 [3.83]	0.66 (0.59 – 0.69)	2.39 [2.26]
Proportion mediated	49.5%		47.6%		13.6%	

Interpretation. *Housing is a mediator at all ages contributing more among adults, followed by children under 5 and least among school-aged children. Housing is the only mediator among adults (16+). Educational attainment, and LLIN use were important mediators among both children under 5 and school-aged children (5-15 years). Good nutrition appears to mediate a small proportion of the effect of SEP on P. falciparum infection only among school-aged children. Mediated effect through nutritional status needs to be interpreted cautiously in light of bidirectional relationship between malaria and anemia that can't be distinguished due to design limitations.*

Supplementary File 6- Distribution of downstream mediators by educational attainment

Additional file 6: Distribution of downstream mediators by educational attainment

	Dry season (Sept/Oct, 2014) (N = 3,223)			Rainy season (Sept/Oct, 2014) (N = 2,988)		
Characteristic	None, N = 601	*Primary,* N = 1896	Post primary, N = 731	None, N = 605	*Primary,* N = 1,668 [1]	Post primary, N = 715
Housing quality						
Low	424(70.5%)	933(49.2%)	136 (18.6%)	402(66.4%)	775(46.5%)	176 (24.6%)
High	177(29.5%)	963 (50.8%)	595 (81.4%)	203(33.6%)	893(53.5%)	539 (75.4%)
Food security						
Less secure	102(17.6%)	247 (17.3%)	47 (6.4 %)	106(17.5%)	299(17.9%)	88 (12.3%)
Secure	478(82.4%)	1,623(86.8%)	684 (93.6%)	499(82.5%)	1,369(82.1%)	626 (87.7%)
Net use (slept in net previous night)						
No	404(67.2%)	1,112(59.2%)	319 (43.6%)	254(42.0%)	579 (34.7%)	218 (30.5%)
Yes	197(32.8%)	774 (40.8%)	412 (56.4%)	351(58.0%)	1089 (65.3%)	497 (69.5%)
Nutritional status (6 months – 15 years)						
Had anemia	182(57.1%)	560 (50.7%)	176 (43.5%)	195(60.9%)	506 (56.4%)	174 (45.4%)
No Anemia	13(42.9%)	545 (49.3%)	229 (56.5%)	125(39.1%)	391 (43.6%)	209 (54.6%)

The table indicates differential distribution of other mediators by educational attainment. Educational attainment which is more upstream mediator appears to correlate (have influence) on more proximal potential mediators of the association between SEP and plasmodium falciparum infection

2.3. Do wealth, education, and urbanicity promote timely healthcare-seeking and diagnostic testing for febrile children? A meta-analysis of 16 national surveys in sub-Saharan Africa.

Do wealth, education, and urbanicity promote timely healthcare - seeking and diagnostic testing for febrile children? A meta-analysis of 16 national surveys in sub-Saharan Africa

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Abstract

Background

Effective and timely management of suspected paediatric malaria is crucial in reducing related mortality in sub-Saharan Africa (SSA). Despite efforts to fight malaria and overcome inequities in accessing related health care and treatment, malaria in children under the age of 5 continues to be a major cause of death. This study re-evaluates the role of poverty, maternal education, and urbanicity in influencing timely healthcare-seeking and diagnostic testing for febrile children.

Methods

Data from nine Demographic and Health Surveys and seven Malaria Indicator Surveys across 16 SSA countries from 2018 to 2023 were individually analysed using modified Poisson regression to assess the association between socioeconomic position (SEP), maternal education and urbanicity, and the outcomes – timely healthcare-seeking and diagnostic testing for suspected paediatric malaria. The estimated Prevalence Ratios (PRs) from the surveys were combined to determine pooled PRs using a random effects meta-analysis. Mediating pathways between SEP and diagnostic testing were explored.

Results

Meta-analysis indicates that only 58.3% of caregivers sought timely medical care for children and 38.2% of all febrile children underwent diagnostic testing. Children from households with medium (PR = 1.09, 95% CI 1.04 – 1.14) and higher SEP (PR = 1.18, 95%CI 1.11 – 1.25) were more likely to receive timely medical attention than those from lower SEP households. Maternal education beyond primary level was associated with timely healthcare-seeking in countries with malaria incidence of ≥ 300 cases per 1,000 population (PR = 1.11, 95%CI 1.01 – 1.23). Additionally, higher SEP was also associated with an increased likelihood of diagnostic testing (PR = 1.15, 95%CI 1.03 – 1.28), with initial healthcare-seeking decision and type of health care (hospital care over primary care) acting as partial mediators. No urban-rural disparities in timely healthcare-seeking and diagnostic testing were observed.

Conclusions

Disparities persist in timely healthcare-seeking and diagnostic testing for suspected paediatric malaria, influenced by SEP and maternal education. It is essential to focus on initiatives that aim to reach those most in need. Enhancing diagnostic services at

primary care levels and adopting integrated interventions that combine individual-level biomedical and behavioural with structural strategies are critical to overcoming these disparities.

Keywords: Socioeconomic disparities, healthcare-seeking behaviour, diagnostic testing, Malaria, DHS/MIS, sub-Saharan Africa.

Introduction

Malaria remains endemic in sub-Saharan Africa (SSA), accounting for over 94% of global malaria cases and deaths. Children under five continue to suffer the highest burden of malaria-related mortality [1]. Fever, a common symptom, is a key indicator for suspected malaria in endemic settings [2]. Timely medical attention, usually within 24 hours of symptom onset is critical for reducing the risk of severe disease and death among these children [3]. Despite this, evidence shows that a high proportion of deaths in malaria-endemic countries occur at home as a result of not getting appropriate medical attention or because care is sought late [4]. In SSA, medical care for suspected malaria is not consistently sought with an estimated 42% of children with febrile illnesses not receiving any medical consultation or treatment Ge, Liang et al. 2023). Even among those who seek medical attention, timeliness remains low and varies widely across countries [5,6]. This delay in healthcare-seeking not only aggravates disease severity but perpetuates malaria transmission within communities [7]. Furthermore, socioeconomic disparities continue to impede the decision to seek timely medical attention, especially for the most vulnerable populations [3,8,9]. Evidence suggests that parents from urban settings, with higher education, and of higher socioeconomic position (SEP) tend to more often seek medical consultation for their febrile children than their counterparts, although, the distribution of these factors varies across countries [10-12].

Healthcare-seeking helps improve treatment outcomes and reduces inappropriate use of presumptive antimalarial drugs, which can encourage antimicrobial resistance [13]. During visits to health care providers, appropriate diagnostic tests, such as malaria tests (rapid diagnostic tests or microscopy), can be performed which enhances surveillance and appropriate drug use [3,14]. Since 2010, the WHO has recommended diagnostic testing for all suspected malaria cases before initiating treatment [2]. By 2020, over 45 countries in SSA had malaria diagnosis policies for all age groups and had invested in wide-scale availability of rapid diagnostic tests and microscopy for malaria [1]. However, a recent pooled analysis indicated that up to 62% of febrile children who sought care did not receive any blood tests, a figure likely higher among those who did not seek care. Disparities related to urbanicity and socioeconomic characteristics continue to affect diagnostic testing for paediatric fevers [12,15].

Since 2015, the RBM partnership has supported several initiatives including the country-led “high burden to high impact” response and “Zero Malaria Starts with Me” campaigns in 10 and 28 high-burden SSA countries respectively [16,17]. As a result, several countries have increased political commitment and financial investments, including a focus on marginalised populations at high risk of malaria, to enhance malaria prevention, and improve health care access and diagnostics. Between 2020 and 2022, for instance, Burkina Faso and Zambia increased annual government funding for malaria by 60% (from $ 61,427,632 to $ 98,492,016) and 95.0% (from $ 17, 097, 249 to $ 33,336,650) respectively. These initiatives partly aimed to mitigate disparities in healthcare-seeking, diagnosis and appropriate treatment[18]. These initiatives also prioritised malaria risk stratification, facilitating targeted interventions in most affected areas and among vulnerable groups such as those with low SEP, to improve access to care, and diagnostic testing services.

While the full extent of the impact of these initiatives may still unfold, a re-evaluation of the hypothesis that SEP, education and urbanicity influence malaria-related health behaviours is needed. Urban residency, which can be a marker for proximity to health care, along with SEP, maternal education, and type of health care (hospital vs. primary care) are recognised as key determinants of diagnostic testing for febrile conditions in children [12,19,20]. The mediating role of initial healthcare-seeking behaviour and type of health care sought in the relationship between SEP and diagnostic testing is still not well understood, underscoring the need to investigate the complexities surrounding healthcare-seeking and diagnostic testing for suspected paediatric malaria in SSA, including exploration of underlying mechanisms. Our study reports findings of the meta-analysis for the association between socioeconomic factors –household SEP, urban residency and maternal education – and timeliness of healthcare-seeking and diagnostic testing for suspected malaria in children under five across 16 SSA countries from 2018 to 2023.

Methods

Study design and setting

We used 16 nationally representative Demographic and Health Surveys (DHS) / Malaria Indicator Surveys (MIS) conducted in SSA over the last five years, from 2018 to 2023. These included 9 DHS and 7 MIS. Surveys were conducted in 16 countries: DHS – Benin, Burkina Faso, Côte d'Ivoire, The Gambia, Ghana, Kenya, Rwanda, Tanzania, and Zambia, MIS –Cameroon, Guinea, Mali, Mozambique, Niger, Nigeria, and Uganda. Our analytical focus was restricted to the last five years to ensure the contemporality and relevance of our findings. The target study population was children under the age of five years, born to women aged 15-49 years within the households selected for these surveys.

Data sources and collection procedures

The DHS and MIS are standardized cross-sectional surveys implemented in a wide range of low- and middle-income countries, including countries in SSA. DHS are typically conducted during the dry season while MIS are typically during the rainy season, which is the peak malaria transmission period [21]. These surveys provide estimates for a multitude of health indicators, which are pivotal for monitoring the progress towards achieving national and international development goals. Indicators assessed include but are not limited to, malaria prevalence, healthcare-seeking behaviour — specifically diagnosis and treatment and coverage of preventive measures. To ensure a representative sample, both DHS and MIS adopt a stratified two-stage cluster sampling methodology in which (i) primary sampling units (PSUs) are randomly selected from census data and (ii) households within PSUs are randomly selected from an updated enumeration list [22].

Our analysis included a weighted sample of 138,712 children aged between 6 to 59 months who were present in the household the night before the survey. The weights were obtained from the women's survey. Data were collected by trained enumerators, who elicited detailed information on child, mother, and household characteristics. Women were asked questions about their children's health, including illness/fever episodes, and subsequent healthcare-seeking decisions.

Measurement of variables

Outcomes: In this study, the main outcomes were timely seeking of healthcare for suspected malaria and malaria diagnostic testing among children with febrile illness. As studies were conducted in known malaria-endemic countries, having had a fever within two weeks before the survey was used as the definition of suspected malaria [23]. According to WHO malaria guidelines [2], care/treatment seeking is considered timely if it occurs within 24 hours of symptom onset from health facilities, pharmacies, medical personnel or other public or private sectors (excluding traditional practitioners). Additionally, the study assessed whether children with febrile illness received a diagnostic blood test using the question "At any time during the illness did (name) have blood taken from their finger or heel for testing?" and responses were dichotomized (yes or no) to facilitate analysis. To avoid misclassification, "Do not know" responses were excluded from the manifest variables. This question does not differentiate between diagnostic tests and is assumed to refer to either microscopy or rapid diagnostic tests.

Exposure: The main socioeconomic factors were household socioeconomic position (SEP) and urbanicity. Households' SEP was asset-based, which is a composite measure reflecting a household's living standard. The index is calculated using principal component analysis (PCA) of data on household ownership of selected assets, including televisions, radios, bicycles, materials for housing construction, types of water access, and sanitation facilities. DHS/MIS have a SEP variable with households categorised into quintiles. For our analysis, quintiles were recategorized into three strata: high (5th quintile), middle (3 and 4th quintile) or low (1st and 2nd quintiles) to improve interpretation. Maternal educational attainment, categorised as primary level or lower (no schooling or completed primary school) and post-primary (completed secondary school, or completed tertiary school/university). Urbanicity was defined in terms of place of residence, either urban or rural.

Covariates. The analysis in individual surveys incorporated covariates, including children's age in months, mother's age in full years, children's sex (male, female), and household size.

Mediators. We assessed the mediating role of healthcare-seeking behaviour (healthcare-seeking vs home or no care). For those who sought care, we tested the mediating role of type of health care (hospital versus primary care). Health care types: hospital versus primary care were generated from responses to the question "Where did you seek advice or treatment?". Hospitals included sources initially classified as public hospitals, private or NGO hospitals while primary care sources included public or private health centres, posts, mobile clinics, community health workers, pharmacies, private doctors, and other public or private sectors. Primary care sources are hierarchically lower-level sources which are initial points of contact for most people, especially for the poor and those in rural areas.

Statistical analysis

We used descriptive statistics to determine the proportions of children under five who experienced a fever episode in the past two weeks, sought timely care, and underwent diagnostic testing. Similar statistics were provided for SEP, urban residency, maternal education, and the sex of the child. Mean was used for continuous data (such as the child's age). The survey design was integrated into the analysis to reflect the population accurately, using individual sample weights for women.

We applied separate generalized estimating equations (GEE) models of the Poisson family with the log link function, an exchangeable correlation structure and a random household slope to assess the association between socioeconomic factors and the outcomes – timely healthcare-seeking, and diagnostic testing. The analysis focused on asset-based SEP, maternal educational attainment and urbanicity as primary exposures, adjusting for the child's sex and age (continuous), and the mother's age (continuous). We calculated individual survey prevalence ratios (PRs) and combined them into pooled PRs using random effects meta-analysis. Subgroup analyses were conducted based on survey type (MIS or DHS) or national malaria incidence rate based on WHO reports [24] (high: ≥300 cases, moderate: 200 to 299 cases, and low: <200 cases per 1000) where appropriate.

Regarding diagnostic testing, we investigated the mediating effects of initial healthcare-seeking behaviour and type of health care (hospital versus primary care) on the association between SEP and diagnostic testing. We reported results - the natural indirect effects (based on the odds ratio scale) and proportion mediated from a regression-based approach [25].

Ethical consideration

This study utilised secondary survey data from which all personal identifiers had been removed. These data are accessible to authorized individuals via online data repositories (www.dhsprogram.com). The DHS Program's procedures and questionnaires have undergone a review process and received approval from the ICF International Institutional Review Board (IRB). Additionally, country-specific DHS survey protocols are reviewed by the ICF IRB and typically by an IRB in the host country. The DHS Program granted explicit permission for the use of these data in our study. Participation in DHS and MIS surveys is based on voluntary written informed consent.

Results

Prevalence of paediatric fever

A total of 16 nationally representative surveys conducted between 2018 and 2023 in SSA were included in the analyses. Analyses revealed variations in the prevalence of paediatric fever over the previous two weeks. The percentage of children under five experiencing fevers ranged from 10.5% in Tanzania to 36.5% in Nigeria (Table 1). Notably, the prevalence was higher in MIS studies (29.9%, 95% CI 26.4 – 33.7) compared to DHS studies (16.6%,95% CI 14.14 – 19.0).

Table 1: Prevalence of fever in previous 2 weeks among children by country

Country	Survey type	Year	Fieldwork months	N	Report of fever in previous 2 weeks (95% CI)
Tanzania	DHS	2022	Feb to Jul	10,496	10.5 (9.9 – 11.1)
Ghana	DHS	2022/23	Oct 2022 to Jan 2023	8,315	15.1 (14.3 – 15.8)
Gambia	DHS	2019/20	Nov 2019 to Mar 2020	7,297	15.1 (14.3 – 16.0)
Zambia	DHS	2018/19	Jul 2018 to Jan 2019	7,294	15.8 (15.1 – 16.6)
Kenya	DHS	2022	Feb to Jul	16,883	17.1 (16.6 – 17.7)
Cote D'Ivoire	DHS	2021	Sep to Dec	9,156	17.3 (16.6 – 18.1)
Rwanda	DHS	2019/20	Nov 2019 to Jul 2020	8,020	18.8 (17.9 – 19.7)
Benin	DHS	2017/18	Nov 2017 to Feb 2018	12,686	19.4 (18.8 – 20.1)
Burkina Faso	DHS	2021	Jul to Dec	11,855	22.2 (21.4 – 23.0)
Pooled (DHS) [1]				94,069	16.6 (14.4 – 19.0)
Guinea	MIS	2021	Jul to Sept	4,005	23.0 (21.7 – 24.3)
Uganda	MIS	2019	Dec 2018 to Jan 2019	6,635	26.6 (25.5 – 27.7)
Mali	MIS	2021	Sep to Nov	9,227	27.2 (26.3 – 27.7)
Mozambique	MIS	2018	Apr to Jun	4,750	31.0 (29.7 – 32.4)
Cameroon	MIS	2022	Aug to Dec	4312	31.0 (29.8 – 32.6)
Niger	MIS	2021	Aug to Oct	4,909	35.3 (33.9 – 36.6)
Nigeria	MIS	2021	Oct to Dec	10,805	36.5 (35.6 – 37.4)
Pooled (MIS) [1]				44,643	29.9 (26.4 – 33.7)
Pooled (All)[1]				138,712	**21.7 (18.2 – 25.8)**

[1]Pooled estimates based on random effects. Abbreviations: CI: Confidence Interval, N: Total number of participants, DHS: Demographic and Health Survey, MIS: Malaria indicator survey.

Healthcare-seeking behaviour

Among children with febrile symptoms, 65.9% sought medical advice or treatment. Uganda had the highest rate of healthcare-seeking at 86.8%, while Benin had the lowest at 53.1%. Of those who sought medical care, 58.3% did so in a timely manner (within 24 hours of symptom onset), in line with the WHO guidelines (Table 2). There was considerable variation in timely healthcare-seeking rates, with Gambia having the highest at 77.7% and Mali the lowest at 40.7% (Table 2).

Diagnostic blood testing for malaria

The proportion of children with fever who had blood drawn for malaria testing also varied, with Burkina Faso reporting the highest proportion (65.2%) and Benin the lowest (17.8%). On average, 38.2% of children in all countries underwent diagnostic testing, as detailed in Table 2.

Table 2: Timely healthcare-seeking and malaria diagnostic testing among children with suspected malaria

Survey	Type	N	Household and maternal characteristics (%)				Child characteristics		Health care seeking and diagnostic testing (%)		
			Urban residence	SEP		Post-primary education	Mean age in months	Female (%)	Sought treatment or advice	Timely health care seeking[2]	Blood drawn for diagnostics
				Middle	High						
Tanzania, 2022	DHS	1,098	29.6	42.0	22.7	25.6	27.9	47.6	78.4	55.3	50.6
Ghana, 2022	DHS	1,252	39.1	35.0	11.4	53.7	29.8	50.0	58.1	57.6	40.5
Gambia, 2020	DHS	1,105	64.7	40.7	15.6	34.0	23.5	46.2	64.2	77.7	27.4
Zambia, 2018	DHS	1,479	28.9	31.0	11.6	34.4	26.0	48.1	77.1	61.6	63.2
Kenya, 2022	DHS	2,890	37.1	39.6	19.6	51.5	27.1	48.9	68.6	60.5	33.5
Cote D'Ivoire, 2021	DHS	1,587	50.1	37.3	16.3	21.2	26.8	50.7	62.5	62.3	38.6
Rwanda, 2020	DHS	1,507	14.1	39.2	14.5	22.4	26.1	48.9	62.3	54.0	40.7
Benin, 2018	DHS	2,466	34.7	42.7	15.7	14.9	26.1	48.0	53.1	52.4	17.8
Burkina Faso, 2021	DHS	2,631	22.8	44.8	15.6	16.9	28.9	49.0	74.8	75.5	65.2
Pooled (DHS) (95%CI)[1]		13,384							66.6 (60.8 – 72.3)	61.9 (56.0 - 67.8)	42.0 (31.7 – 52.2)
Guinea, 2021	MIS	921	27.2	40.4	16.0	16.6	27.8	46.3	61.1	52.6	28.1
Uganda, 2019	MIS	1,764	13.0	36.4	7.6	18.0	27.0	47.8	86.8	66.1	51.6
Mali, 2021	MIS	2,513	20.4	41.4	18.5	18.2	27.8	46.5	60.0	40.7	23.4
Mozambique, 2018	MIS	1,474	24.2	34.3	10.6	18.5	26.7	49.8	68.5	52.2	48.0
Cameroon, 2022	MIS	1343	40.8	32.5	12.2	37.1	28.2	46.8	55.7	57.1	26.7
Niger, 2021	MIS	1,731	11.0	43.6	13.2	8.4	27.9	48.5	67.0	57.8	32.2
Nigeria, 2021	MIS	3,947	24.2	37.2	14.6	34.1	29.5	48.0	62.8	50.6	24.4
Pooled (MIS) (95%CI)[1]		16,324							66.0 (58.5 – 70.8)	53.8 (48.0 - 59.7)	33.5 (24.9 - 42.0)
Overall (95%CI)[1]		29,708							66.3 (61.9 – 70.8)	58.4 (53.8 - 62.9)	38.2 (31.3 – 45.2)

[1]Pooled estimates based on random effects, [2] Subset of those who sought care.

Abbreviations: CI: Confidence Interval, N: Total number of participants, DHS: Demographic and Health Survey, MIS: Malaria indicator survey, SEP: Socioeconomic position.

Associations between socioeconomic indicators and timely healthcare-seeking

The study indicated that children from the middle (PR = 1.09, 95% CI 1.04 – 1.14) and higher socioeconomic strata (PR = 1.18, 95%CI 1.11 – 1.26) were more likely to access timely health care compared to those from households of lower socioeconomic strata. This trend was observed in both DHS and MIS surveys with a marginally stronger effect noted in MIS (Table 3). For detailed country-specific estimates, see supplementary file 1a.

Regarding maternal education (beyond primary school level), a positive association with timely healthcare-seeking was noted in specific countries such as Burkina Faso (PR = 1.10, 95% CI 1.03 – 1.18), Mali (PR = 1.23,95%CI 1.03 – 1.46), and Nigeria (PR = 1.30,95%CI 1.15 – 1.46). The positive association was also significant in countries with a malaria incidence of ≥ 300 cases per 1,000 population (PR = 1.11, 95%CI 1.01 – 1.23). However, the combined estimate from all countries showed no significant association with timely healthcare-seeking (OR = 1.04, 95%CI = 1.00 – 1.10) (Table 3). For more details, refer to supplementary file 1b. Living in urban areas was not associated with timely healthcare-seeking (PR = 1.01, 95%CI 0.96 – 1.06), as detailed in supplementary file 1c.

Associations between socioeconomic indicators and diagnostic testing

The analysis indicated that children from higher SEP households were 15% more likely to get tested for malaria than their counterparts from lower SEP households (PR = 1.15, 95%CI 1.03 – 1.28). This disparity was more evident in DHS surveys (PR = 1.16, 95%CI 1.01 – 1.34) than in MIS surveys (PR = 1.12, 95%CI 0.93 – 1.35) (Table 2). For detailed effects of SEP on diagnostic testing by country, see supplementary file 2a. Maternal education beyond primary level was not associated with diagnostic test utilization (PR = 1.07, 95%CI 0.98 – 1.16) (Table 3), with country-specific associations detailed in supplementary file 2b. Additionally, urban residency was also not associated with the likelihood of undergoing diagnostic testing (supplementary file 2c)

Table 3: Association between socioeconomic Indicators and timely healthcare-seeking and diagnostic testing for suspected Malaria

Variable	Categories	Timely health care seeking PR (95%CI)			Diagnostic testing PR (95%CI)		
		DHS	**MIS**	**Pooled**	**DHS**	**MIS**	**Pooled**
Residence	Rural	1	1	1	1	1	1
	Urban	1.02 (0.96 – 1.08)	1.01 (0.91 – 1.12)	1.01 (0.96 – 1.06)	0.97 (0.88 – 1.07)	0.98 (0.89– 1.06)	0.96 (0.91 – 1.10)
Household SEP	Lower	1	1	1	1	1	1
	Middle	1.06 (1.01 – 1.10)	1.15 (1.06 – 1.25)	1.09 (1.04 – 1.14)	1.03 (0.94 – 1.14)	1.04 (0.94 – 1.16)	1.04 (0.97 – 1.11)
	Higher	1.17 (1.08 – 1.26)	1.20 (1.07 – 1.34)	1.18 (1.11 – 1.25)	1.16 (1.01 – 1.34)	1.12 (0.93 – 1.35)	1.15 (1.03 – 1.28)
Mothers education	Primary school or lower	1	1	1	1	1	1
	Secondary school and higher	1.05 (1.01 – 1.10)	1.05 (0.92 – 1.19)	1.04 (1.00 – 1.10)	1.05 (0.98 – 1.12)	1.09 (0.89 – 1.34)	1.07 (0.98 – 1.16)

Note: Individual survey models adjusted for mother's age, household size, age and sex of the child; Abbreviations: CI: Confidence Intervals. DHS: Demographic and Health Survey, MIS: Malaria indicator survey, PR: Prevalence Ratio, SEP: Socioeconomic position.

Mediation analysis

Initial healthcare-seeking behaviour

Our analysis of the indirect effects of SEP on diagnostic testing utilization revealed that SEP plays a significant role in influencing healthcare-seeking which consequently increases the likelihood of being tested. This was evident in 81.3% (**13/16)** of the surveys except Tanzania, Ghana and the Gambia. In Zambia (direct effect: OR = 0.54, 95%CI 0.34 – 0.61), Kenya (direct effect: OR= 0.83,95%CI 0.81 – 0.97), Uganda (direct effect: OR =0.72, 95%CI 0.62 – 0.82), Niger (direct effect: OR =0.72, 95%CI 0.65 – 0.81) and Nigeria (direct effect: OR= 0.78, 95%CI 0.53 – 0.90), a higher SEP appears to be associated with lower odds of diagnostic testing (Table 3).

Table 3: Mediated effects of SEP on diagnostic test uptake through healthcare-seeking behaviour

Variable	Survey type	Direct effect OR (95% CI)	Indirect effect OR (95%CI)	**Potential mediation**
Tanzania, 2022	DHS	1.28 (1.06 – 1.55)	1.06 (0.96 – 1.07)	No
Ghana, 2022	DHS	0.73 (0.72 – 1.01)	1.05 (0.84 – 1.17)	No
Gambia, 2020	DHS	1.27 (1.03 – 2.22)	1.08 (0.97 – 1.21)	No
Zambia, 2018	DHS	0.54 (0.34 – 0.61) [1]	**1.22 (1.08 – 1.27)**	Yes
Kenya, 2022	DHS	0.83 (0.81 – 0.97) [1]	**1.21(1.18 – 1.23)**	Yes
Cote D'Ivoire, 2021	DHS	1.08 (0.72 – 1.60)	**1.36 (1.32 – 1.56)**	Yes
Rwanda, 2020	DHS	1.29 (1.00 – 1.43)	**1.76 (1.58 - 1.88)**	Yes
Benin, 2018	DHS	0.90 (0.74 – 1.01)	**1.49 (1.44 – 1.51)**	Yes
Burkina Faso, 2021	DHS	1.03 (0.81 – 1.10)	**1.24 (1.20 – 1.42)**	Yes
Guinea, 2021	MIS	0.81 (0.70 – 1.01)	**1.39 (1.31 – 1.55)**	Yes
Uganda, 2019	MIS	0.72 (0.62 – 0.82) [1]	**1.06 (1.03 – 1.12)**	Yes
Mali, 2021	MIS	0.99 (0.81 – 1.29)	**1.37 (1.21 – 1.41)**	Yes
Mozambique, 2018	MIS	0.70 (0.56 – 1.00)	**1.77 (1.46 – 1.80)**	Yes
Cameroon, 2022	MIS	1.27 (1.00 – 1.66)	**1.19 (1.06 – 1.45)**	Yes
Niger, 2021	MIS	0.72 (0.65 – 0.81) [1]	**1.06 (1.01 – 1.09)**	Yes
Nigeria, 2021	MIS	0.78 (0.53 – 0.90) [1]	**1.12 (1.08 – 1.16)**	Yes

Note: All mediated models adjusted for age and sex of the child and location and active value for exposure (SEP) was modelled as "High" and control value as "Low". Abbreviations: OR: Odds Ratio, CI: Confidence Intervals. [1] Direct effects are counterintuitive.

Type of health care (hospital versus primary care)

Our study also explored whether the type of health care acts as a mediator in the relationship between SEP and the probability of receiving diagnostic tests. Our analysis indicates that SEP has an indirect effect on diagnostic testing through the chosen type of health care, with this mediation effect evident in 13 of the 15 surveys. In contrast, in Uganda (OR = 0.89, 95%CI 0.84 – 0.91) and Ghana (OR = 0.92 95%CI 0.84 – 0.94) opting for hospital care was associated with an 11% reduction in the odds of undergoing diagnostic tests, as presented in Table 4. Mozambique was not included as none of the participants sought care at hospitals.

Table 4: Mediating role of hospital versus primary care (only those who sought care)

Variable	Survey type	Direct effect (95% CI)	Indirect effect (95%CI)	**Potential mediation**
Tanzania, 2022	DHS	1.17 (0.72 – 1.33)	**1.14 (1.13 – 1.22)**	Yes
Ghana, 2022	DHS	0.55 (0.45 – 0.56)	**1.13 (1.01 – 1.18)**	Yes
Gambia, 2020	DHS	1.10 (0.71 – 1.82)	**1.08 (1.06 – 1.23)**	Yes
Zambia, 2018	DHS	0.36 (0.27 – 0.49)	**1.04 (1.02 – 1.08)**	Yes
Kenya, 2022	DHS	0.61 (0.82 – 0.97)	**1.20 (1.12 – 1.22)**	Yes
Cote D'Ivoire, 2021	DHS	0.91 (0.77 – 1.03)	**1.05 (1.02 – 1.07)**	Yes
Rwanda, 2020	DHS	1.38 (0.99 – 1.58)	1.01 (0.96 – 1.02)	No
Benin, 2018	DHS	0.82 (0.76 – 1.24)	**1.06 (1.04 – 1.10)**	Yes
Burkina Faso, 2021	DHS	0.99 (0.79 – 1.22)	**1.02 (1.01 – 1.04)**	Yes
Guinea, 2021	MIS	0.76 (0.81 – 1.01)	0.92 (0.84 – 0.94)	Yes[1]
Uganda, 2019	MIS	0.76 (0.66 – 1.10)	0.92 (0.91 – 0.98)	Yes[1]
Mali, 2021	MIS	0.85 (0.71 – 1.33)	**1.04 (1.03 – 1.07)**	Yes
Cameroon, 2022	MIS	1.016 (0.74 – 1.17)	**1.38 (1.14 – 1.64)**	Yes
Niger, 2021	MIS	1.44 (1.04 – 1.804)	1.01 (0.99 – 1.02)	No
Nigeria, 2021	MIS	0.72 (0.64 – 0.83)	**1.18 (1.15 – 1.24)**	Yes

Note: All mediated models adjusted for the child's age, sex and location and active value for exposure was modelled as "High" and control value as "Low". Abbreviations: OR: Odds Ratio, CI: Confidence Intervals. [1] Potential mediator but effects are counterintuitive.

Discussion

In SSA, where malaria is endemic, timely healthcare-seeking and diagnostic testing are crucial for the effective management of paediatric fevers. Our study revealed a high prevalence of fever, with rates ranging from 10.5% to 36.5%. Notably, there was high variability in timely healthcare-seeking (40.7% to 77.7%), and diagnostic testing (17.8% to 65.2%) across countries. This study specifically assessed the effects of widely acknowledged socioeconomic barriers to care — particularly household SEP, maternal education and urbanicity, and tried to thereby assess if progress has been made against the backdrop of recent large-scale initiatives to reduce malaria mortality and morbidity in SSA.

Our findings reinforce the significant role of socioeconomic disparities in shaping health care behaviours. Belonging to a middle or higher SEP stratum was associated with timely health care seeking, with caregivers in these groups being 9% and 18% more likely to seek prompt medical attention, respectively. This aligns with previous studies [12,26,27], which also highlighted SEP disparities in timely health care utilization. However, we observe smaller disparities than previously reported which we hypothesize may be influenced by recent investments in malaria control initiatives. Despite primary health care services being free of charge in most countries, barriers such as diagnostic and medication shortages, and long waiting times persist, disproportionately affecting caregivers with lower SEP. These barriers not only delay treatment but also exacerbate health inequities, as highlighted in previous studies [28,29]. Critical barriers remain, such as the cost of transportation and medication, which may require out-of-pocket money not readily available leading to delayed treatment-seeking [30,31]. Furthermore, in SSA, caregivers with lower SEP backgrounds face competing concerns, such as the opportunity costs of not working whilst seeking care [32].

The effect of maternal education on timely health care seeking was not strong overall, except in Burkina Faso, Mali, and Nigeria. Notably, in countries with malaria incidence of ≥300 cases per 1,000, caregivers with secondary education or higher were more proactive in seeking timely care, reflecting a context-dependent effect of education. Previous studies have shown that in high transmission settings, a higher proportion of fevers can be attributed to malaria with more educated mothers perceiving those risks and seeking health care in a shorter period of time [33,34]. These findings are consistent with other studies [30,35] which showed a positive association between maternal/caregiver education attainment and timely health care seeking in high endemic settings.

Higher SEP was also associated with an increased likelihood of febrile children undergoing diagnostic testing, consistent with other studies in SSA [20,26]. Crucially, the study identified the type of health care sought as a key mediator of the association between SEP and diagnostic testing. Caregivers from higher SEP backgrounds are more likely to seek care at better-equipped health care facilities, such as hospitals, which tend to offer more comprehensive diagnostic services. Whereas most countries, except Nigeria and Cameroon, have free-of-charge diagnostic testing policies, the regular shortages of diagnostics in primary care settings can hinder diagnostic testing [18]. This is particularly concerning because families of lower socio-economic strata in more remote settings often seek care at such facilities[36]. This underscores the importance of addressing structural barriers to health care access, as highlighted in the literature[37].

The increasing trend of parents bypassing primary health care facilities in favour of pharmacies is complicating timely malaria diagnoses[38]. Bypassing primary health care is often motivated by factors, such as convenience, shorter waiting times, and the immediate availability of medications [39]. This behaviour can lead to delayed malaria diagnosis, as pharmacies may not have the necessary diagnostic tools and tend to provide symptomatic treatment instead [40,41]. This trend reflects a critical gap in the programs implemented where accessibility, perceived quality of care, and trust in primary health care facilities are lacking, driving caregivers to seek alternative, albeit suboptimal, solutions. However, this practice undermines efforts to ensure timely and accurate malaria diagnosis, delaying appropriate treatment, and potentially exacerbating the disease's impact on children.

Our findings have to be understood against the backdrop of major malaria control programs, such as the RBM initiative and Integrated Community Case Management (iCCM). The RBM partnership has been instrumental in scaling up the use of insecticide-treated nets (ITNs), indoor residual spraying (IRS), and rapid diagnostic tests (RDTs), while iCCM has trained community health workers (CHWs) to deliver care in hard-to-reach areas [42]. Despite these advancements, our study highlights ongoing challenges, particularly regarding socioeconomic disparities in health care utilization. Given the mechanisms described, potential interventions could focus on ensuring the availability of diagnostics in all primary care and private facilities (or subsidizing them). This approach mitigates opportunity costs and the direct cost of diagnostics, making diagnostic testing accessible to all children. Our findings underscore the need for interventions to promote healthcare-seeking behaviours, especially among populations in need and promote access and availability to malaria diagnostic testing at primary health care levels. Emerging evidence also points to the transformative potential of economic interventions in breaking the malaria-poverty cycle. Microfinance initiatives have shown remarkable success in empowering families to invest in malaria prevention measures and improving their economic stability[43]. These programs empower local populations to take charge of their health, fostering resilience and sustainability in malaria control efforts. This bottom-up approach, as opposed to traditional top-down methods, recognizes the vital role of communities in the fight against malaria.

One of the strengths of this study lies in the scope and rigour of the meta-analysis, which is based on data from large nationally representative surveys. Unlike most secondary analyses, which use estimates from inconsistently adjusted models, our analyses are robust because they have been carefully conducted on individual survey data and adjusted for the same covariates across different models. Moreover, the data are also aggregated from multiple datasets, resulting in a large sample size that allows for more precise estimates. The data are also recent, which means that the findings have timely implications in light of large-scale interventions introduced around post-2015. However, the study is not without limitations. Notably, the absence of certain contextual and behavioural factors in the DHS/MIS surveys limits our ability to explain surprising findings such as the indirect effect of SEP on diagnostic testing observed in Guinea and Uganda. This means some underlying pathways could not be explored and other confounders could not be well adjusted for. Consequently, this gap points to the need for more complementary data collection approaches that can capture these critical dimensions. Secondly, the classification of shops and markets—establishments that usually lack diagnostic testing—as primary care may lead to an overestimation of the mediating role of hospital care. Nevertheless, this overestimation is expected to be marginal, given that such facilities account for less than 5% of patient visits, thereby minimizing their influence within the primary care classification

Conclusions

We observed suboptimal healthcare-seeking behaviour (timeliness of health care seeking) and diagnostic testing. Despite initiatives implemented after 2015, disparities in timely healthcare-seeking and access to malaria diagnostic testing based on SEP, though they were of lesser magnitude than those reported in DHS/MIS surveys conducted before 2018. While the effects of these interventions may become more apparent over time, monitoring progress provides relevant evidence to guide ongoing national and regional efforts. The SEP disparities in diagnostic testing were found to be partly mediated by the initial healthcare-seeking behaviour and the type of health care sought. Maternal education was associated with timely healthcare-seeking only in high-incidence countries while urbanicity (urban residency) did not play a role. To address these challenges, targeted initiatives must incorporate a multifaceted integrated approach that combines structural elements, such as providing relevant diagnostics and medications, especially at primary care centres, with individual-level factors, such as awareness-raising and behavioural initiatives aimed at caregivers to improve risk perception and encourage timely healthcare-seeking.

Declarations

Ethical considerations

Not applicable because this study utilised secondary, non-identifiable survey data, which is accessible to authorized individuals via online data repositories.

Data availability

The datasets are available on the DHS Program
https://dhsprogram.com/data/available-datasets.cfm upon request.

Funding Statement

The author(s) received no specific funding for this work.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

STW, EL and DIP conceived the study. STW curated and analysed data and initiated manuscript writing. EL reviewed the analysis. EL, JM, MML, DM and DIP provided a critical review of the manuscript. All authors read and approved the manuscript.

Acknowledgements

Not applicable.

Consent for publication

Not applicable.

References

1. WHO. World malaria report 2020: 20 years of global progress and challenges. 2020. https://apps.who.int/iris/rest/bitstreams/1321872/retrieve (accessed 8 April 2022.
2. WHO. WHO guidelines for malaria , 13 July 2021. Geneva: World Health Organization, 2021.
3. WHO. Global technical strategy for malaria 2016-2030. Geneva: World Health Organization; 2015.
4. Jaiteh F, Okebe J, Masunaga Y, et al. Understanding adherence to reactive treatment of asymptomatic malaria infections in The Gambia. *Sci Rep* 2021; **11**(1): 1746.
5. Hamooya BM, Chongwe G, Dambe R, Halwiindi H. Treatment-seeking behaviour for childhood fever among caretakers of Chivuna and Magoye rural communities of Mazabuka District, Zambia: a longitudinal study. *BMC Public Health* 2016; **16**(1): 762.
6. Musoke D, Ndejjo R, Wafula ST, Kasasa S, Nakiyingi-Miiro J, Musoke MB. Malaria health seeking practices for children, and intermittent preventive treatment in pregnancy in Wakiso District, Uganda. *Afr Health Sci* 2021; **21**(4): 1722-32.
7. Van Malderen C, Amouzou A, Barros AJD, Masquelier B, Van Oyen H, Speybroeck N. Socioeconomic factors contributing to under-five mortality in sub-Saharan Africa: a decomposition analysis. *BMC Public Health* 2019; **19**(1): 760.
8. Adedokun ST, Yaya S. Factors influencing mothers' health care seeking behaviour for their children: evidence from 31 countries in sub-Saharan Africa. *BMC Health Services Research* 2020; **20**(1): 842.
9. Yaya S, Odusina EK, Adjei NK. Health care seeking behaviour for children with acute childhood illnesses and its relating factors in sub-Saharan Africa: evidence from 24 countries. *Trop Med Health* 2021; **49**(1): 95.
10. Ng'ambi W, Mangal T, Phillips A, et al. Factors associated with healthcare seeking behaviour for children in Malawi: 2016. *Trop Med Int Health* 2020; **25**(12): 1486-95.
11. Cassy A, Saifodine A, Candrinho B, et al. Care-seeking behaviour and treatment practices for malaria in children under 5 years in Mozambique: a secondary analysis of 2011 DHS and 2015 IMASIDA datasets. *Malar J* 2019; **18**(1): 115.
12. Ge Y, Liang D, Cao J, Gosling R, Mushi V, Huang J. How socioeconomic status affected the access to health facilities and malaria diagnosis in children under five years: findings from 19 sub-Saharan African countries. *Infect Dis Poverty* 2023; **12**(1): 29.
13. Rathmes G, Rumisha SF, Lucas TC, et al. Global estimation of anti-malarial drug effectiveness for the treatment of uncomplicated Plasmodium falciparum malaria 1991–2019. *Malaria journal* 2020; **19**: 1-15.
14. WHO. Updated WHO recommendations for malaria chemoprevention and elimination. 2022.
15. Macarayan E, Papanicolas I, Jha A. The quality of malaria care in 25 low-income and middle-income countries. *BMJ Glob Health* 2020; **5**(2): e002023.
16. WHO. High burden to high impact: a targeted malaria response: World Health Organization, 2018.
17. African Union, ALMA, RBM. African Union Malaria Status Report 2022, 2023.
18. WHO. World malaria report 2023: World Health Organization, 2023.
19. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: a barrier to effective health care. *Clinical Infectious Diseases* 2006; **42**(3): 377-82.
20. Johansson EW, Gething PW, Hildenwall H, et al. Diagnostic Testing of Pediatric Fevers: Meta-Analysis of 13 National Surveys Assessing Influences of Malaria Endemicity and Source of Care on Test Uptake for Febrile Children under Five Years. *PLOS ONE* 2014; **9**(4): e95483.
21. MEASURE, DHS, PMI, RBM, UNICEF, WHO. Household survey indicators for malaria control. 2018.
22. ICF International. DHS methodology. 2017. http://dhsprogram.com/What-We-Do/Survey-Types/DHS-Methodology.cfmMay 15, 2024).

23. Rios-Zertuche D, Carter KH, Harris KP, et al. Performance of passive case detection for malaria surveillance: results from nine countries in Mesoamerica and the Dominican Republic. *Malaria Journal* 2021; **20**(1): 208.
24. WHO. Incidence of malaria (per 1,000 population at risk) - Sub-Saharan Africa. 2024. https://data.worldbank.org/indicator/SH.MLR.INCD.P3?locations=ZG (accessed June 20, 2024.
25. Shi B, Choirat C, Coull BA, VanderWeele TJ, Valeri L. CMAverse: A Suite of Functions for Reproducible Causal Mediation Analyses. *Epidemiology* 2021; **32**(5): e20-e2.
26. Schoeps A, Gabrysch S, Niamba L, Sié A, Becher H. The Effect of Distance to Health-Care Facilities on Childhood Mortality in Rural Burkina Faso. *American Journal of Epidemiology* 2011; **173**(5): 492-8.
27. Wafula ST, Habermann T, Franke MA, et al. What are the pathways between poverty and malaria in sub-Saharan Africa? A systematic review of mediation studies. *Infect Dis Poverty* 2023; **12**(1): 58.
28. Lungu EA, Biesma R, Chirwa M, Darker C. Healthcare seeking practices and barriers to accessing under-five child health services in urban slums in Malawi: a qualitative study. *BMC Health Services Research* 2016; **16**(1): 410.
29. Hanson K, Brikci N, Erlangga D, et al. The Lancet Global Health Commission on financing primary health care: putting people at the centre. *The Lancet Global Health* 2022; **10**(5): e715-e72.
30. Stanley CC, Chirombo J, Msuku H, et al. Prompt treatment-seeking behaviour varies within communities among guardians of children with malaria-related fever in Malawi. *Malar J* 2023; **22**(1): 246.
31. Romay-Barja M, Cano J, Ncogo P, et al. Determinants of delay in malaria care-seeking behaviour for children 15 years and under in Bata district, Equatorial Guinea. *Malar J* 2016; **15**: 187.
32. Abegaz NT, Berhe H, Gebretekle GB. Mothers/caregivers healthcare seeking behavior towards childhood illness in selected health centers in Addis Ababa, Ethiopia: a facility-based cross-sectional study. *BMC Pediatr* 2019; **19**(1): 220.
33. Wang SJ, Lengeler C, Smith TA, et al. Rapid urban malaria appraisal (RUMA) in sub-Saharan Africa. *Malar J* 2005; **4**: 40.
34. Thwing JI, Mihigo J, Fernandes AP, et al. How much malaria occurs in urban Luanda, Angola? A health facility-based assessment. *Am J Trop Med Hyg* 2009; **80**(3): 487-91.
35. Alga A, Wasihun Y, Ayele T, Endawkie A, Feleke SF, Kebede N. Factors influencing delay in malaria treatment seeking at selected public health facilities in South Gonder, Ethiopia. *Scientific Reports* 2024; **14**(1): 6648.
36. Nabyonga Orem J, Mugisha F, Okui AP, Musango L, Kirigia JM. Health care seeking patterns and determinants of out-of-pocket expenditure for malaria for the children under-five in Uganda. *Malar J* 2013; **12**: 175.
37. Carrillo JE, Carrillo VA, Perez HR, Salas-Lopez D, Natale-Pereira A, Byron AT. Defining and targeting health care access barriers. *J Health Care Poor Underserved* 2011; **22**(2): 562-75.
38. Lamshöft MM, Liheluka E, Ginski G, et al. Understanding pre-hospital disease management of fever and diarrhoea in children—Care pathways in rural Tanzania. *Tropical Medicine & International Health* 2024; **n/a**(n/a).
39. Alqossayir FM, Alkhowailed MS, Alammar AY, Alsaeed AA, Alamri YY, Rasheed Z. Factors associated with patients bypassing primary healthcare centres in Qassim Region, KSA. *Journal of Taibah University Medical Sciences* 2021; **16**(6): 900-5.
40. Nsengimana A, Isimbi J, Uwizeyimana T, et al. Malaria rapid diagnostic tests in community pharmacies in Rwanda: availability, knowledge of community pharmacists, advantages, and disadvantages of licensing their use. *Glob Health Res Policy* 2023; **8**(1): 40.
41. Kizito J, Kayendeke M, Nabirye C, Staedke SG, Chandler CI. Improving access to health care for malaria in Africa: a review of literature on what attracts patients. *Malar J* 2012; **11**: 55.

42. Oliphant NP, Manda S, Daniels K, et al. Integrated community case management of childhood illness in low- and middle-income countries. *Cochrane Database of Systematic Reviews* 2021; (2).
43. Yoshino CA, Sidney-Annerstedt K, Wingfield T, et al. Experiences of conditional and unconditional cash transfers intended for improving health outcomes and health service use: a qualitative evidence synthesis. *Cochrane Database of Systematic Reviews* 2023; (3).

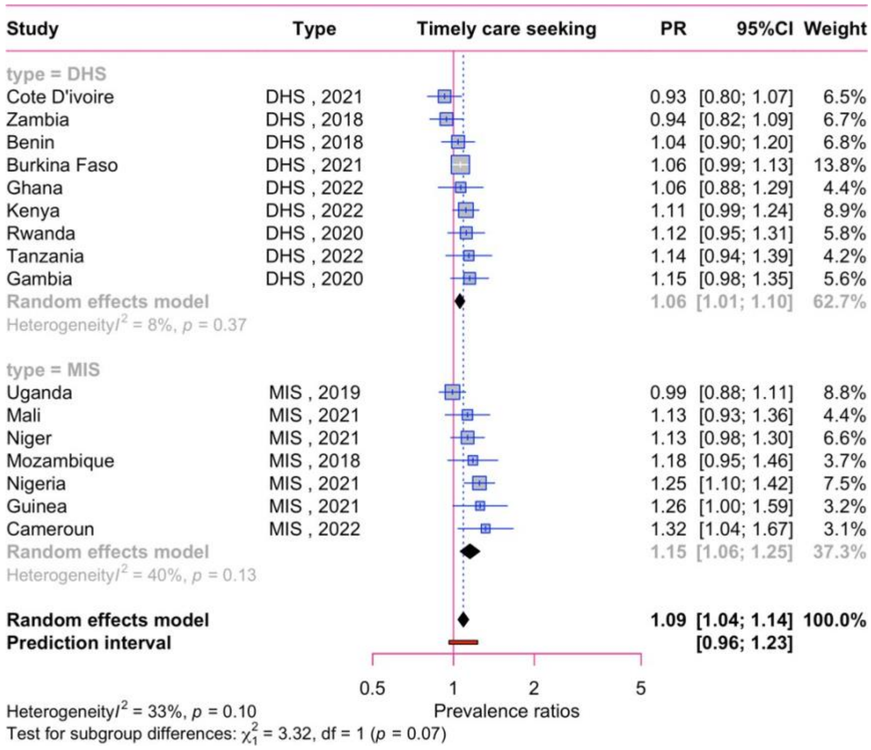
Supplementary files

a. Supplementary File 1: SEP and timely healthcare-seeking.

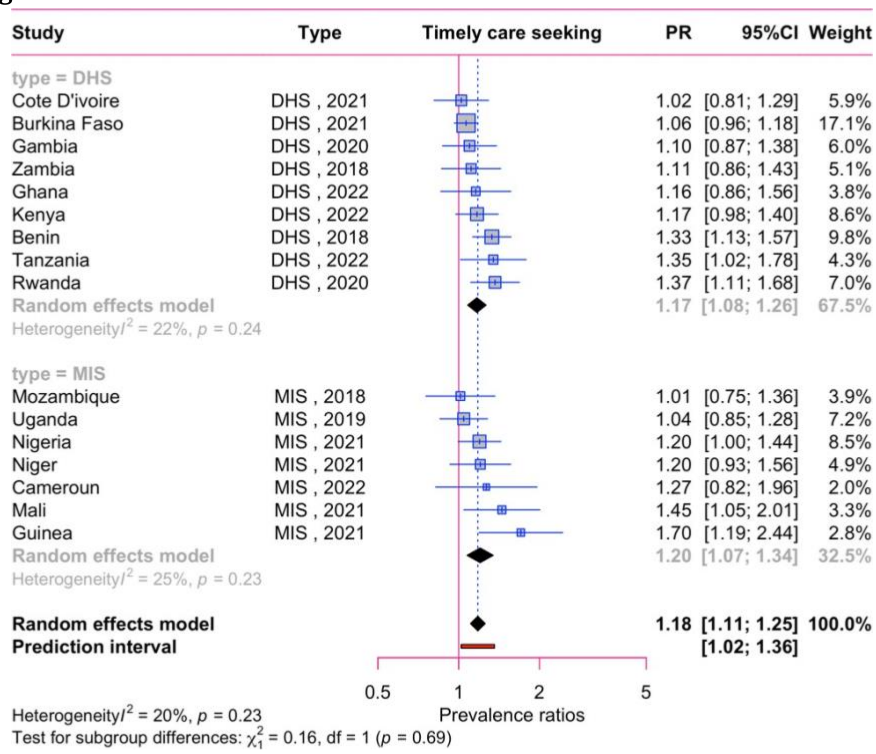
A positive association was observed between middle (PR = 1.09, 95%CI 1.04 – 1.14) and higher SEP (PR = 1.18, 95%CI 1.11 – 1.25) and timely healthcare-seeking (S. Fig 1a).

S. Fig 1a. Association between SEP and timely care seeking

1) Middle versus Low SEP



2. High versus Low SEP



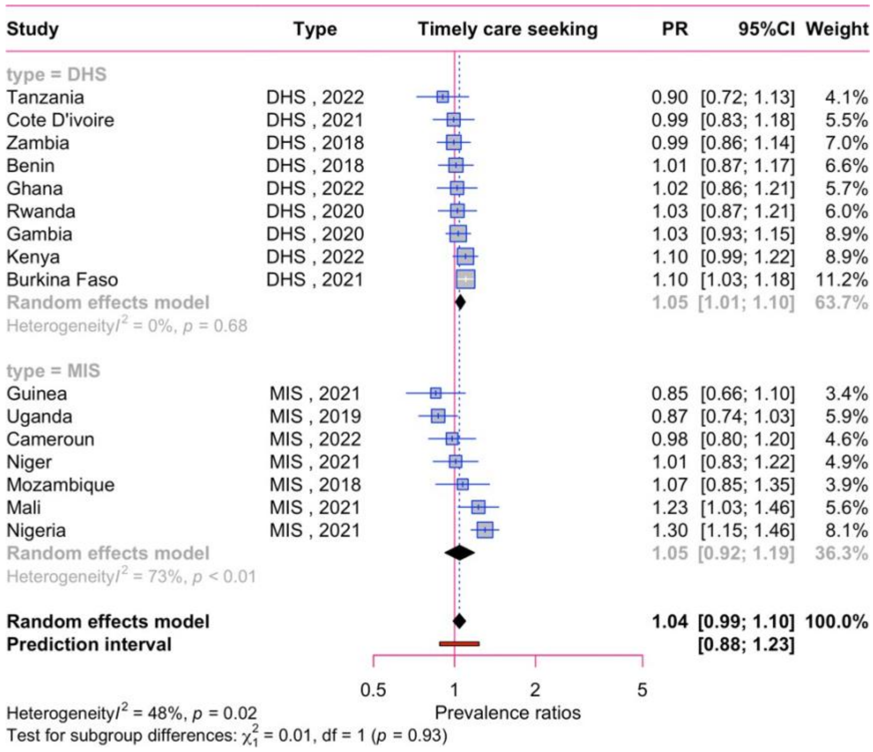
Note: All models adjusted for sex, age, residence, household size, and mothers age, and maternal education

b. Supplementary File 1b: Maternal education and timely healthcare-seeking

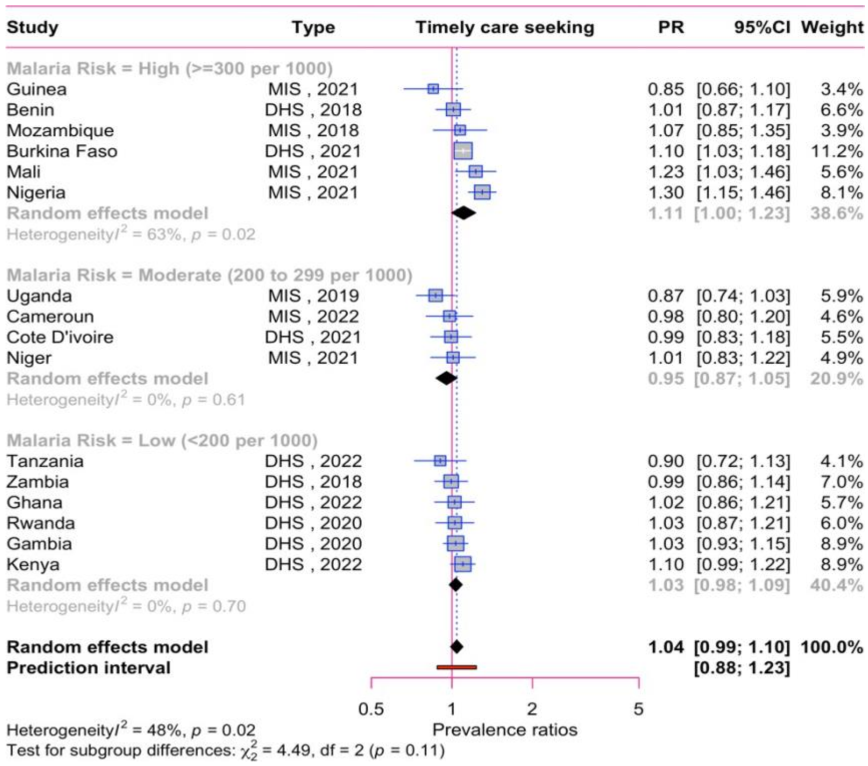
Here, the pooled estimates indicate no association between maternal education beyond primary education and timely healthcare-seeking for their children. However, in DHS surveys (PR = 1.05, 96%CI 1.01 – 1.10) and high incidence countries, there is small effect of maternal education on timely healthcare -seeking (PR = 1.107, 95%CI 1.002 – 1.228)

S. Fig 1b. Association between maternal education and timely healthcare-seeking

a) **Stratified by survey type**



b) **Stratified by malaria incidence rate**

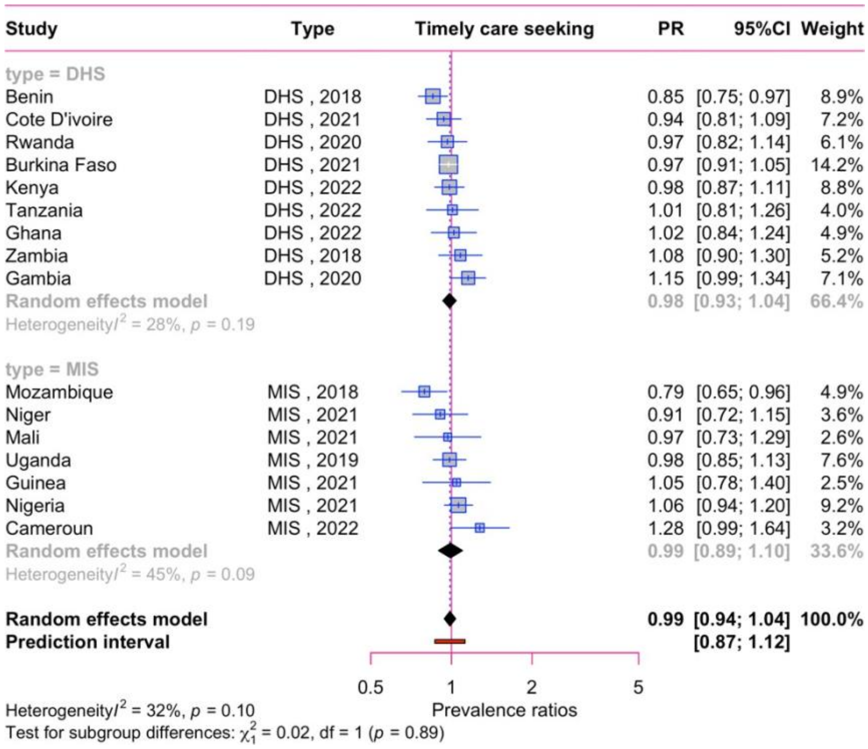


Note: All models adjusted for sex, age, residence, household size, and mothers age, and SEP

Supplementary file 1c: Rural residence and timely healthcare-seeking

Living in a rural versus urban was not associated with timely healthcare-seeking across all countries (S.Fig 2c)

S. Fig 1c. Association between rural residence and timely care seeking



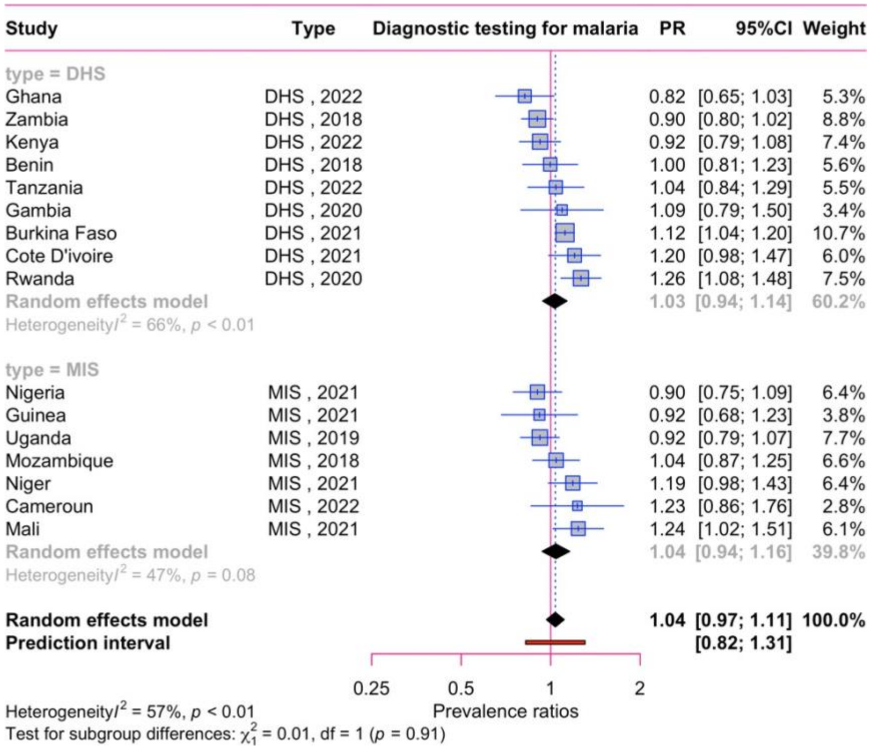
Note: All models adjusted for sex, age, household size, and mothers age, maternal education and SEP

Supplementary file 2a: Association between SEP and diagnostic testing

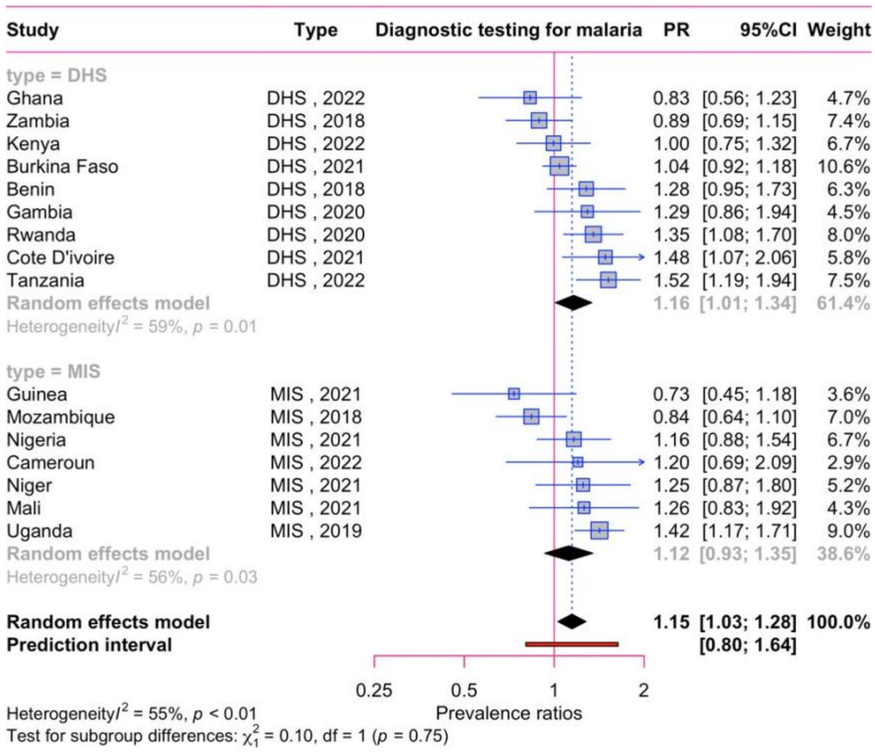
Higher SEP was associated with higher likelihood of receiving diagnostic test among febrile children (PR = 1.15, 95%CI 1.03 – 1.28) and the trend was more evident in DHS surveys.

S. Fig 2a. Association between SEP and diagnostic testing

1) **Middle versus Low SEP**



1) **High versus Low SEP**

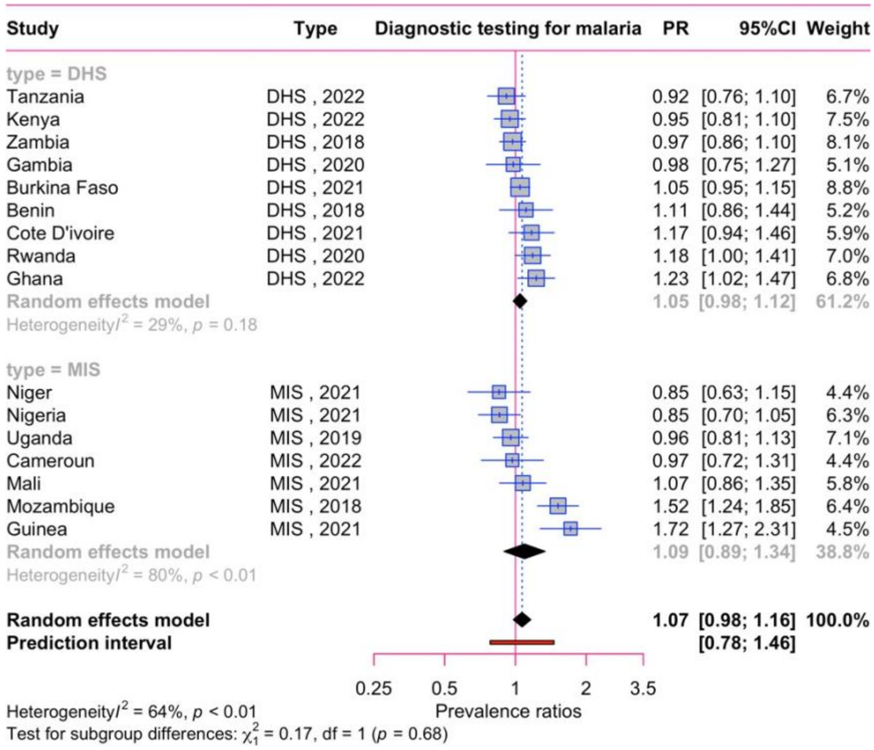


Note: All models adjusted for sex, age, residence, household size, and mothers age, and maternal education

Supplementary file 2b: Association between maternal education and diagnostic testing

In Ghana (PR = 1.23, 95%CI 1.02 – 1.47), Mozambique (PR = 1.52, 95%CI 1.24 – 1.85) and Guinea (PR = 1.72, 95%CI 1.27 – 2.31), a positive association between maternal education beyond primary level and diagnostic testing among children. Pooled estimates indicate no association between maternal education and diagnostic testing for paediatric fevers (PR = 1.07, 95%CI 0.98 – 1.16) (S. Fig 2b).

S. Fig 2b. Association between maternal education and diagnostic testing

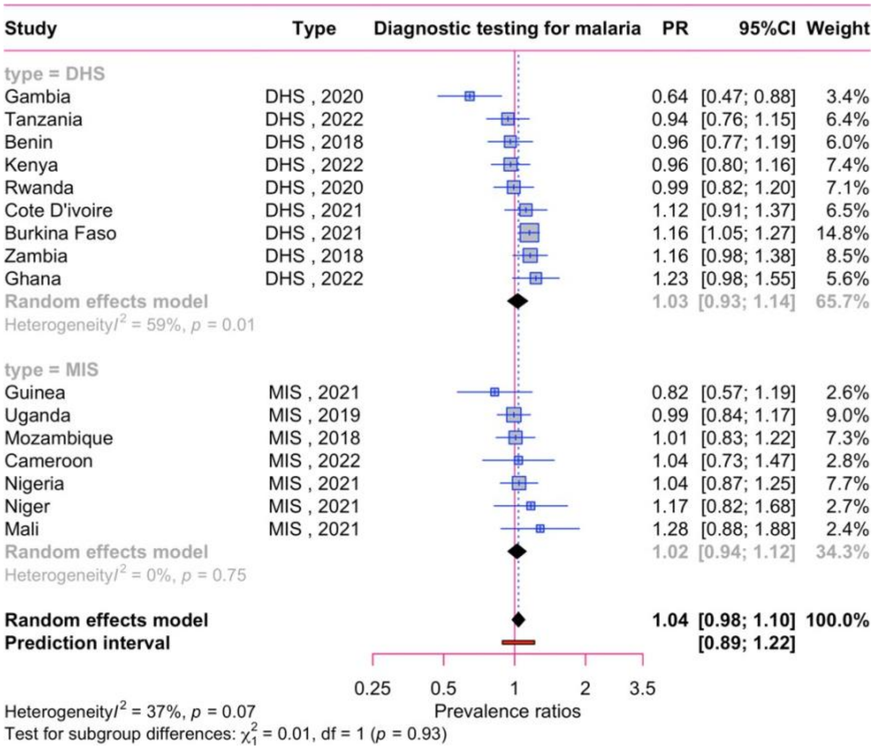


Note: Models adjusted for sex, age, household size, and mothers age, SEP and residence type

Supplementary file 2c: Association between rural residence and diagnostic testing

Meta analysis shows no association between staying in rural settings and diagnostic testing (PR = 1.04, 95%CI 0.98 – 1.10)

S. Fig 2c. Association between rural residence and diagnostic testing



Note: Models adjusted for sex, age, household size, and mothers age, SEP and maternal education

3.0 Summary

3.1 English

Malaria remains a leading cause of morbidity and mortality, with an estimated 249 million infections and 608,000 deaths recorded in 2022 alone. Over 94% of these cases and deaths occurred in sub-Saharan Africa (SSA). Despite progress in malaria prevention and control in SSA over the past two decades, socioeconomic disparities in malaria incidence and healthcare-seeking behaviour for febrile illnesses persist both at regional and national levels.

This thesis is structured around three main components. First, a systematic review was conducted to examine the pathways linking poverty and malaria in SSA, focusing on studies that used mediation analysis, or reported changes in the coefficients of potential mediating variables in models adjusted for socioeconomic position (SEP) and mediators. The review appraised the mediation methods used and highlighted their strengths and limitations (Paper I). In Paper II, we used a regression-based counterfactual approach to mediation analysis in order to investigate the structural mechanisms driving socioeconomic disparities in *P. falciparum* infection, drawing on secondary data from two large cross-sectional studies conducted in the Southern region of Malawi during the dry and rainy seasons of 2014. This analysis presented the total natural direct effects (TNDEs) of SEP, the total natural indirect effects (TNIEs) through the mediator(s), and the proportion mediated (PM). In Paper III, we assessed the association between socioeconomic factors – SEP, maternal educational attainment and urban residence – and timely healthcare-seeking and diagnostic testing in children under five with febrile illness. A random-effects meta-analysis was conducted, using prevalence ratios (PRs) and standard errors from 16 nationally representative surveys conducted between 2018 and 2023. We also examined the mediating role of health facility type in the association between SEP and diagnostic testing.

In the systematic review (Paper I), we identified mediators, such as improved food security, better housing quality, and previous antimalarial use, while factors such as secondary or higher education of maternal/household head, use of long-lasting insecticide treated nets (LLINs), better nutrition, and indoor residual spraying were suggested as potential protective mediators based on changes in coefficients. In paper II, using data from cross-sectional surveys conducted in Malawi, housing (TNIE, OR =

0.54, 95%CI 0.49 – 0.63) and educational attainment of the household head (TNIE, OR = 0.73, 95%CI 0.67 – 0.81) were identified as mediators of the association between SEP and *P. falciparum* infection during the rainy season. During the dry season, housing (TNIE, OR = 0.63, 95%CI 0.59 – 0.64), educational attainment (TNIE, OR = 0.70, 95%CI 0.62 – 0.71) and LLIN use (TNIE, OR = 0.88, 95%CI 0.85 – 0.94) were important mediators. In Paper III, the results of the meta-analysis revealed that only 58.3% of febrile children received timely healthcare, and 38.2% underwent diagnostic testing. Higher SEP was associated with timely healthcare-seeking (PR = 1.18, 95%CI 1.11 – 1.25) and diagnostic testing (PR = 1.15, 95%CI 1.03 – 1.28). Higher maternal education was associated with timely healthcare-seeking in countries with malaria incidence ≥ 300 per 1,000 persons (PR = 1.11, 95%CI 1.01 – 1.23). Urban residence did not play a role in healthcare-seeking and diagnostic testing. The type of healthcare attended mediated the effect of SEP on diagnostic testing, with hospital visits (versus primary care) being associated with a higher likelihood of receiving diagnostic testing in 14 of 15 surveys.

The findings presented clearly show that the socioeconomic situation of a population is significantly associated with malaria risk, with evidence on the mediating factors being particularly useful in guiding policy and programs on where to focus their efforts. Key priorities should include improving housing conditions, enhancing education or malaria prevention awareness and training, in combination with ensuring widespread distribution and correct use of LLINs to reduce malaria infection rates.

Additionally, the socioeconomic inequalities in healthcare-seeking behaviours highlight the need for targeted efforts to mitigate barriers to healthcare access, such as providing subsidies to families with low SEP. Finally, improving diagnostic supplies and the quality of primary care services can significantly improve diagnostic testing and timely appropriate care for children with febrile illnesses.

3.2. German

Malaria ist nach wie vor eine der Hauptursachen für Morbidität und Mortalität. Allein im Jahr 2022 wurden schätzungsweise 249 Millionen Infektionen und 608.000 Todesfälle registriert. Mehr als 94 % dieser Fälle und Todesfälle traten in Afrika südlich der Sahara (SSA) auf. Trotz der Fortschritte bei der Malariaprävention und -kontrolle in SSA in den letzten zwei Jahrzehnten gibt es nach wie vor Unterschiede in der Malariainzidenz und dem Gesundheitsverhalten bei fieberhaften Erkrankungen, sowohl auf nationaler als auch auf Haushaltsebene.

Diese Arbeit gliedert sich in drei Hauptkomponenten. Zunächst wurde eine systematische Übersichtsarbeit durchgeführt, um den Zusammenhang zwischen Armut und Malaria in SSA zu untersuchen. Der Schwerpunkt lag dabei auf Studien, die Mediationsanalysen verwendeten oder über Änderungen der Koeffizienten potenzieller Mediationsvariablen in Modellen berichteten, die für SEP und Mediatoren adjustiert waren. Die Übersichtsarbeit bewertete die verwendeten Mediationsmethoden systematisch und hob ihre Stärken und Grenzen hervor (Papier I). In Paper II untersuchten wir die strukturellen Mechanismen, die sozioökonomische Ungleichheiten bei Infektionen mit *P. falciparum* verursachen, indem wir einen regressionsbasierten kontrafaktischen Ansatz für die Mediationsanalyse verwendeten. Wir stützten uns dabei auf Sekundärdaten aus zwei großen Querschnittsstudien, die in Malawi während der Trocken- und Regenzeit 2014 durchgeführt wurden. Diese Analyse präsentierte die gesamten natürlichen direkten Effekte (TNDEs) von SEP, die gesamten natürlichen indirekten Effekte (TNIEs) durch den/die Mediator(en) und den mediierten Anteil (PM). In Paper III untersuchten wir den Zusammenhang zwischen sozioökonomischen Faktoren – SEP, mütterlicher Bildungsgrad und städtischer Wohnort – und rechtzeitiger Gesundheitsversorgung und diagnostischen Tests für Kinder unter fünf Jahren mit fieberhaften Erkrankungen. Es wurde eine Metaanalyse mit zufälligen Effekten unter Verwendung von Prävalenzverhältnissen (PRs) und Standardfehlern aus 16 landesweit repräsentativen Erhebungen durchgeführt, welche zwischen 2018 und 2023 stattfanden. Wir untersuchten auch die Rolle der Art der Gesundheitseinrichtung als Mediator im Zusammenhang zwischen SEP und diagnostischen Tests.

In der systematischen Übersichtsarbeit (Artikel I) identifizierten wir Mediatoren wie Ernährungssicherheit, Wohnverhältnisse und vorherige Verwendung von Malariamedikamenten, während Faktoren wie die Bildungsgrad der Mutter/des

Haushaltsvorstands, langlebige insektizidbehandelte Moskitonetze (LLINs), Ernährung und Insektizidbehandlungen von Innenräumen aufgrund von Änderungen von Koeffizienten als potenzielle Mediatoren vorgeschlagen wurden. In Artikel II wurden anhand von Daten aus Malawi die Wohnraumqualität (TNIE, OR = 0,54, 95 % KI 0,49 – 0,63) und das Bildungsniveau des Haushaltsvorstands (TNIE, OR = 0,73, 95 % KI 0,67 – 0,81) als Mediatoren des Zusammenhangs zwischen SEP und *P. falciparum*-Infektion während der Regenzeit identifiziert. Während der Trockenzeit waren die Wohnverhältnisse (TNIE, OR = 0,63, 95 % KI 0,59 – 0,64), Bildung (TNIE, OR = 0,70, 95 % KI 0,62 – 0,71) und LLINs (TNIE, OR = 0,88, 95 % KI 0,85 – 0,94) wichtige Mediatoren. In Artikel III zeigten die Ergebnisse der Metaanalyse, dass nur 58,3 % der fiebrigen Kinder rechtzeitig ärztlich versorgt wurden und 38,2 % diagnostische Tests erhielten. Ein höherer SEP war mit rechtzeitiger medizinischer Versorgung (PR = 1,18, 95 % KI 1,11 – 1,25) und diagnostischen Tests (PR = 1,15, 95 % KI 1,03 – 1,28) assoziiert. Ein höheres Bildungsniveau der Mutter war in Ländern mit einer Malariainzidenz von ≥ 300 pro 1000 Personen mit einer rechtzeitigen medizinischen Versorgung verbunden (PR = 1,11, 95 % KI 1,01 – 1,23). Der städtische Wohnort spielte keine Rolle für die medizinische Versorgung und diagnostisches Testen. Die Art der Gesundheitseinrichtung mediierte den Zusammenhang zwischen SEP und dem diagnostischen Testen, wobei Krankenhausbesuche (im Vergleich zur Primärversorgung) in 14 von 15 Erhebungen mit einer höheren Wahrscheinlichkeit für diagnostische Tests verbunden waren.

Die vorgestellten Ergebnisse zeigen deutlich, dass die sozioökonomische Situation einer Bevölkerung maßgeblich mit dem Malariarisiko zusammenhängt. Die Erkenntnisse über die vermittelnden Faktoren sind besonders hilfreich bei der Orientierung von Politik und Programmen, worauf sich ihre Bemühungen konzentrieren sollten. Zu den wichtigsten Prioritäten sollten die Verbesserung der Wohnverhältnisse, die Verbesserung der Bildung oder Aufklärungsprogramme zur Malariaprävention, in Kombination mit der Gewährleistung einer weit verbreiteten Verteilung und korrekten Verwendung von LLINs gehören, um die Malariainfektionsraten zu senken.

Darüber hinaus unterstreichen die sozioökonomischen Ungleichheiten im Gesundheitsverhalten die Notwendigkeit gezielter Anstrengungen zum Abbau von Hindernissen für den Zugang zur Gesundheitsversorgung, wie z.B. die Bereitstellung von Subventionen für Familien mit niedrigem SEP. Schließlich kann eine

Verbesserung der diagnostischen Möglichkeiten und der Qualität der Leistungen in der primären Gesundheitsversorgung die rechtzeitige und angemessene Diagnose und Behandlung von Kindern mit fieberhaften Erkrankungen erheblich verbessern.

4.0. References

1. WHO. World malaria report 2023: World Health Organization, 2023.
2. Ferrari AJ, Santomauro DF, Aali A, et al. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2013;2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet* 2024; **403**(10440): 2133-61.
3. Andrade MV, Noronha K, Diniz BPC, et al. The economic burden of malaria: a systematic review. *Malar J* 2022; **21**(1): 283.
4. Weiss DJ, Lucas TCD, Nguyen M, et al. Mapping the global prevalence, incidence, and mortality of Plasmodium falciparum, 2000-17: a spatial and temporal modelling study. *Lancet* 2019; **394**(10195): 322-31.
5. WHO. Global technical strategy for malaria 2016-2030. Geneva: World Health Organization; 2015.
6. Weiss DJ, Bertozzi-Villa A, Rumisha SF, et al. Indirect effects of the COVID-19 pandemic on malaria intervention coverage, morbidity, and mortality in Africa: a geospatial modelling analysis. *Lancet Infect Dis* 2021; **21**(1): 59-69.
7. Sato S. Plasmodium-a brief introduction to the parasites causing human malaria and their basic biology. *J Physiol Anthropol* 2021; **40**(1): 1.
8. Haldar K, Bhattacharjee S, Safeukui I. Drug resistance in Plasmodium. *Nat Rev Microbiol* 2018; **16**(3): 156-70.
9. Chu CS, White NJ. Management of relapsing Plasmodium vivax malaria. *Expert Rev Anti Infect Ther* 2016; **14**(10): 885-900.
10. Sylla K, Tine R, Sow D, et al. Anemia, Thrombocytopenia, and Changes in Biochemical Parameters Occurring in Patients with Uncomplicated Plasmodium falciparum Malaria: Data Analysis from Antimalarial Efficacy-Randomized Trials in Dakar and Kaolack Regions, Senegal. *J Parasitol Res* 2022; **2022**: 1635791.
11. Rouamba T, Samadoulougou S, Ouédraogo M, Hien H, Tinto H, Kirakoya-Samadoulougou F. Asymptomatic malaria and anaemia among pregnant women during high and low malaria transmission seasons in Burkina Faso: household-based cross-sectional surveys in Burkina Faso, 2013 and 2017. *Malar J* 2021; **20**(1): 211.
12. Uneke CJ, Sunday-Adeoye I, Iyare FE, Ugwuja EI, Duhlinska DD. Impact of maternal Plasmodium falciparum malaria and haematological parameters on pregnancy and its outcome in southeastern Nigeria. *J Vector Borne Dis* 2007; **44**(4): 285-90.
13. Mohandas N, An X. Malaria and human red blood cells. *Med Microbiol Immunol* 2012; **201**(4): 593-8.
14. Bartoloni A, Zammarchi L. Clinical aspects of uncomplicated and severe malaria. *Mediterr J Hematol Infect Dis* 2012; **4**(1): e2012026.
15. WHO. WHO guidelines for malaria , 13 July 2021. Geneva: World Health Organization, 2021.
16. Makenga G, Baraka V, Francis F, et al. Effectiveness and safety of intermittent preventive treatment with dihydroartemisinin-piperaquine or artesunate-amodiaquine for reducing malaria and related morbidities in schoolchildren in Tanzania: a randomised controlled trial. *The Lancet Global Health* 2023; **11**(8): e1277-e89.
17. Orok AB, Ajibaye O, Aina OO, Iboma G, Adagyo Oboshi S, Iwalokun B. Malaria interventions and control programes in Sub-Saharan Africa: A narrative review. *Cogent Medicine* 2021; **8**(1): 1940639.
18. Makenga G, Seth MD, Baraka V, et al. Implementation research of a cluster randomized trial evaluating the implementation and effectiveness of intermittent preventive treatment for

malaria using dihydroartemisinin-piperaquine on reducing malaria burden in school-aged children in Tanzania: methodology, challenges, and mitigation. *Malar J* 2023; **22**(1): 7.
19. Teklehaimanot, Paola Mejia A. Malaria and Poverty. *Ann N Y Acad Sci* 2008; **1136**(1): 32-7.
20. Tusting LS, Rek J, Arinaitwe E, et al. Why is malaria associated with poverty? Findings from a cohort study in rural Uganda. *Infect Dis Poverty* 2016; **5**(1): 78.
21. Cibulskis RE, Alonso P, Aponte J, et al. Malaria: Global progress 2000 - 2015 and future challenges. *Infect Dis Poverty* 2016; **5**(1): 61.
22. Sarma N, Patouillard E, Cibulskis RE, Arcand JL. The Economic Burden of Malaria: Revisiting the Evidence. *Am J Trop Med Hyg* 2019; **101**(6): 1405-15.
23. UNDP. Human Development Report 2011. Sustainability and Equity: A better future for all, 2011.
24. Our World in Data. Malaria prevalence vs gdp-per-capita. 2023. https://ourworldindata.org/grapher/malaria-prevalence-vs-gdp-per-capita#:~:text=Malaria%20prevalence%20is%20the%20share%20of16th September 2024).
25. WHO. World malaria report 2012, 2012.
26. Worrall E, Basu S, Hanson K. Is malaria a disease of poverty? A review of the literature. *Tropical Medicine & International Health* 2005; **10**(10): 1047-59.
27. Degarege A, Fennie K, Degarege D, Chennupati S, Madhivanan P. Improving socioeconomic status may reduce the burden of malaria in sub Saharan Africa: A systematic review and meta-analysis. *PloS one* 2019; **14**(1): e0211205.
28. Tusting LS, Willey B, Lucas H, et al. Socioeconomic development as an intervention against malaria: a systematic review and meta-analysis. *Lancet* 2013; **382**(9896): 963-72.
29. O'Meara WP, Mangeni JN, Steketee R, Greenwood B. Changes in the burden of malaria in sub-Saharan Africa. *Lancet Infect Dis* 2010; **10**(8): 545-55.
30. Ranson H, N'Guessan R, Lines J, Moiroux N, Nkuni Z, Corbel V. Pyrethroid resistance in African anopheline mosquitoes: what are the implications for malaria control? *Trends Parasitol* 2011; **27**(2): 91-8.
31. Mwaiswelo RO, Mmbando BP, Chacky F, et al. Malaria infection and anemia status in under-five children from Southern Tanzania where seasonal malaria chemoprevention is being implemented. *PloS one* 2021; **16**(12): e0260785.
32. Wanzirah H, Tusting LS, Arinaitwe E, et al. Mind the gap: house structure and the risk of malaria in Uganda. *PLoS One* 2015; **10**(1): e0117396.
33. Tusting LS, Ippolito MM, Willey BA, et al. The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. *Malar J* 2015; **14**: 209.
34. Kahabuka C, Kvåle G, Hinderaker SG. Factors associated with severe disease from malaria, pneumonia and diarrhea among children in rural Tanzania - a hospital-based cross-sectional study. *BMC Infect Dis* 2012; **12**: 219-.
35. Wafula ST, Mendoza H, Nalugya A, Musoke D, Waiswa P. Determinants of uptake of malaria preventive interventions among pregnant women in eastern Uganda. *Malar J* 2021; **20**(1): 5-.
36. Kooko R, Wafula ST, Orishaba P. Socioeconomic determinants of malaria prevalence among under five children in Uganda: Evidence from 2018-19 Uganda Malaria Indicator Survey. *J Vector Borne Dis* 2023; **60**(1): 38-48.
37. Pryce J, Medley N, Choi L. Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. *Cochrane Database Syst Rev* 2022; **1**(1): CD012688.
38. Hamooya BM, Chongwe G, Dambe R, Halwiindi H. Treatment-seeking behaviour for childhood fever among caretakers of Chivuna and Magoye rural communities of Mazabuka District, Zambia: a longitudinal study. *BMC Public Health* 2016; **16**(1): 762.

39. Musoke D, Ndejjo R, Wafula ST, Kasasa S, Nakiyingi-Miiro J, Musoke MB. Malaria health seeking practices for children, and intermittent preventive treatment in pregnancy in Wakiso District, Uganda. *Afr Health Sci* 2021; **21**(4): 1722-32.
40. Ge Y, Liang D, Cao J, Gosling R, Mushi V, Huang J. How socioeconomic status affected the access to health facilities and malaria diagnosis in children under five years: findings from 19 sub-Saharan African countries. *Infect Dis Poverty* 2023; **12**(1): 29.
41. Rathmes G, Rumisha SF, Lucas TC, et al. Global estimation of anti-malarial drug effectiveness for the treatment of uncomplicated Plasmodium falciparum malaria 1991–2019. *Malaria journal* 2020; **19**: 1-15.
42. WHO. High burden to high impact: a targeted malaria response: World Health Organization, 2018.
43. African Union, ALMA, RBM. African Union Malaria Status Report 2022, 2023.
44. Effective Public Health Practice P. Quality assessment tool for quantitative studies. Hamilton: Effective Public Health Practice Project, 1998.
45. Walldorf JA, Cohee LM, Coalson JE, et al. School-Age Children Are a Reservoir of Malaria Infection in Malawi. *PLOS ONE* 2015; **10**(7): e0134061.
46. Cohee LM, Goupeyou-Youmsi J, Seydel KB, et al. Understanding the Intransigence of Malaria in Malawi. *Am J Trop Med Hyg* 2022; **107**(4_Suppl): 40-8.
47. Mathanga DP, Walker ED, Wilson ML, Ali D, Taylor TE, Laufer MK. Malaria control in Malawi: current status and directions for the future. *Acta Trop* 2012; **121**(3): 212-7.
48. Valeri L, Vanderweele TJ. Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods* 2013; **18**(2): 137-50.
49. Shi B, Choirat C, Coull BA, VanderWeele TJ, Valeri L. CMAverse: A Suite of Functions for Reproducible Causal Mediation Analyses. *Epidemiology* 2021; **32**(5): e20-e2.
50. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med* 2017; **167**(4): 268-74.
51. de Glanville WA, Thomas LF, Cook EAJ, et al. Household socio-economic position and individual infectious disease risk in rural Kenya. *Sci Rep* 2019; **9**(1): 2972.
52. VanderWeele TJ, Mumford SL, Schisterman EF. Conditioning on intermediates in perinatal epidemiology. *Epidemiology* 2012; **23**(1): 1-9.
53. Ma C, Claude KM, Kibendelwa ZT, Brooks H, Zheng X, Hawkes M. Is maternal education a social vaccine for childhood malaria infection? A cross-sectional study from war-torn Democratic Republic of Congo. *Pathog Glob Health* 2017; **111**(2): 98-106.
54. Mathanga DP, Halliday KE, Jawati M, et al. The High Burden of Malaria in Primary School Children in Southern Malawi. *Am J Trop Med Hyg* 2015; **93**(4): 779-89.
55. Sakwe N, Bigoga J, Ngondi J, et al. Relationship between malaria, anaemia, nutritional and socio-economic status amongst under-ten children, in the North Region of Cameroon: A cross-sectional assessment. *PloS one* 2019; **14**(6): e0218442.
56. Snyman K, Mwangwa F, Bigira V, et al. Poor housing construction associated with increased malaria incidence in a cohort of young Ugandan children. *Am J Trop Med Hyg* 2015; **92**(6): 1207-13.
57. Ssempiira J, Nambuusi B, Kissa J, et al. Geostatistical modelling of malaria indicator survey data to assess the effects of interventions on the geographical distribution of malaria prevalence in children less than 5 years in Uganda. *PLoS One* 2017; **12**(4): e0174948.
58. Zgambo M, Mbakaya BC, Kalembo FW. Prevalence and factors associated with malaria parasitaemia in children under the age of five years in Malawi: A comparison study of the 2012 and 2014 Malaria Indicator Surveys (MISs). *PloS one* 2017; **12**(4): e0175537.
59. Skarbinski J, Mwandama D, Luka M, et al. Impact of Health Facility-Based Insecticide Treated Bednet Distribution in Malawi: Progress and Challenges towards Achieving Universal Coverage. *PLoS One* 2011; **6**(7): e21995.

60. Skarbinski J, Mwandama D, Wolkon A, et al. Impact of indoor residual spraying with lambda-cyhalothrin on malaria parasitemia and anemia prevalence among children less than five years of age in an area of intense, year-round transmission in Malawi. *Am J Trop Med Hyg* 2012; **86**(6): 997-1004.
61. West PA, Protopopoff N, Rowland M, et al. Malaria risk factors in North West Tanzania: the effect of spraying, nets and wealth. *PloS one* 2013; **8**(6): e65787.
62. Asante KP, Owusu-Agyei S, Cairns M, et al. Placental malaria and the risk of malaria in infants in a high malaria transmission area in ghana: a prospective cohort study. *J Infect Dis* 2013; **208**(9): 1504-13.
63. Liu JX, Bousema T, Zelman B, et al. Is Housing Quality Associated with Malaria Incidence among Young Children and Mosquito Vector Numbers? Evidence from Korogwe, Tanzania. *PLoS One* 2014; **9**(2): e87358.
64. Coleman M, Coleman M, Mabaso ML, et al. Household and microeconomic factors associated with malaria in Mpumalanga, South Africa. *Trans R Soc Trop Med Hyg* 2010; **104**(2): 143-7.
65. Mmbando BP, Kamugisha ML, Lusingu JP, et al. Spatial variation and socio-economic determinants of Plasmodium falciparum infection in northeastern Tanzania. *Malar J* 2011; **10**: 145-.
66. De Beaudrap P, Nabasumba C, Grandesso F, et al. Heterogeneous decrease in malaria prevalence in children over a six-year period in south-western Uganda. *Malar J* 2011; **10**: 132-.
67. Sonko ST, Jaiteh M, Jafali J, et al. Does socio-economic status explain the differentials in malaria parasite prevalence? Evidence from The Gambia. *Malar J* 2014; **13**: 449-.
68. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986; **51**(6): 1173.
69. Huho B, Briët O, Seyoum A, et al. Consistently high estimates for the proportion of human exposure to malaria vector populations occurring indoors in rural Africa. *Int J Epidemiol* 2013; **42**(1): 235-47.
70. Wafula ST, Habermann T, Franke MA, et al. What are the pathways between poverty and malaria in sub-Saharan Africa? A systematic review of mediation studies. *Infect Dis Poverty* 2023; **12**(1): 58.
71. Chanda E, Mzilahowa T, Chipwanya J, et al. Scale-up of integrated malaria vector control: lessons from Malawi. *Bull World Health Organ* 2016; **94**(6): 475-80.
72. Emina JBO, Doctor HV, Yé Y. Profiling malaria infection among under-five children in the Democratic Republic of Congo. *PloS one* 2021; **16**(5): e0250550.
73. Wanzira H, Katamba H, Okullo AE, Agaba B, Kasule M, Rubahika D. Factors associated with malaria parasitaemia among children under 5 years in Uganda: a secondary data analysis of the 2014 Malaria Indicator Survey dataset. *Malaria journal* 2017; **16**(1): 191-.
74. Monroe A, Moore S, Okumu F, et al. Methods and indicators for measuring patterns of human exposure to malaria vectors. *Malar J* 2020; **19**(1): 207.
75. Schoeps A, Gabrysch S, Niamba L, Sié A, Becher H. The Effect of Distance to Health-Care Facilities on Childhood Mortality in Rural Burkina Faso. *American Journal of Epidemiology* 2011; **173**(5): 492-8.
76. Lungu EA, Biesma R, Chirwa M, Darker C. Healthcare seeking practices and barriers to accessing under-five child health services in urban slums in Malawi: a qualitative study. *BMC Health Services Research* 2016; **16**(1): 410.
77. Hanson K, Brikci N, Erlangga D, et al. The Lancet Global Health Commission on financing primary health care: putting people at the centre. *The Lancet Global Health* 2022; **10**(5): e715-e72.
78. Wang SJ, Lengeler C, Smith TA, et al. Rapid urban malaria appraisal (RUMA) in sub-Saharan Africa. *Malar J* 2005; **4**: 40.

79. Thwing JI, Mihigo J, Fernandes AP, et al. How much malaria occurs in urban Luanda, Angola? A health facility-based assessment. *Am J Trop Med Hyg* 2009; **80**(3): 487-91.
80. Stanley CC, Chirombo J, Msuku H, et al. Prompt treatment-seeking behaviour varies within communities among guardians of children with malaria-related fever in Malawi. *Malar J* 2023; **22**(1): 246.
81. Alga A, Wasihun Y, Ayele T, Endawkie A, Feleke SF, Kebede N. Factors influencing delay in malaria treatment seeking at selected public health facilities in South Gonder, Ethiopia. *Scientific Reports* 2024; **14**(1): 6648.
82. Johansson EW, Gething PW, Hildenwall H, et al. Diagnostic Testing of Pediatric Fevers: Meta-Analysis of 13 National Surveys Assessing Influences of Malaria Endemicity and Source of Care on Test Uptake for Febrile Children under Five Years. *PLOS ONE* 2014; **9**(4): e95483.
83. Nabyonga Orem J, Mugisha F, Okui AP, Musango L, Kirigia JM. Health care seeking patterns and determinants of out-of-pocket expenditure for malaria for the children under-five in Uganda. *Malar J* 2013; **12**: 175.
84. Carrillo JE, Carrillo VA, Perez HR, Salas-Lopez D, Natale-Pereira A, Byron AT. Defining and targeting health care access barriers. *J Health Care Poor Underserved* 2011; **22**(2): 562-75.
85. Oliphant NP, Manda S, Daniels K, et al. Integrated community case management of childhood illness in low- and middle-income countries. *Cochrane Database of Systematic Reviews* 2021; (2).

5.0 : List of abbreviations

Pf	*Plasmodium falciparum*
DAG	Directed Acyclic Graph
WHO	World Health Organization
DHS	Demographic and Health Surveys
MIS	Malaria Indicator Surveys
SEP	Socioeconomic Position
SES	Socioeconomic status
PR	Prevalence Ratio
CI	Confidence Intervals
TNDE	Total Natural Direct Effect
TNIE	Total Natural Indirect Effect
LLINs	Long- Lasting Insecticide treated Nets
EPHPP	Effective Public Health Practice Project
IRS	Indoor Residual Spraying
GEE	Generalised Estimating Equations
RDT	Rapid Diagnostic Test
PCA	Principal Component Analysis
PC	Principal Component
SSA	sub-Saharan Africa
ICEMR	International Center of Excellence for Malaria Research
IRB	Institutional Review Board
SAC	School Age Children

6.0 List of figures

7.0 List of tables

8.0 Declaration of personal Contribution

The thesis incorporates previously published materials in manuscript format, cited as follows:

Paper I:

Wafula ST, Habermann T, Franke MA, May J, Puradiredja DI, Lorenz E, Brinkel J. What are the pathways between poverty and malaria in sub-Saharan Africa? A systematic review of mediation studies. Infect Dis Poverty. 2023 Jun 8;12(1):58. https://doi.org/10.1186/s40249-023-01110-2. PMID: 37291664; PMCID: PMC10249281.

In relation to this paper, the co-author contributions were as follows:

- JB, DIP, EL and **STW**: Designed and coordinated the study
- THH, MAF and **STW** spearheaded the review, including conducting database searches, screening review articles, updating the review and critically appraising articles
- **STW** drafted the manuscript
- JB, JM, EL and DIP: Critically reviewed the draft manuscript
- EL, JB, DIP and JM: Provided support and mentorship during the development and writing of the review
- All authors read and approved the final manuscript

Paper II:

Wafula ST, Maiga-Ascofare O, Struck N, Mathanga DP, Cohee LM, May J, Puradiredja DI, Lorenz E. Socioeconomic disparities in *Plasmodium falciparum* infection risk in Southern Malawi: Mediation analyses. *Sci Rep* ***14****, 27290 (2024). https://doi.org/10.1038/s41598-024-78512-1*

Contributions for Paper II were as follows:

- **STW**, LMC and EL conceived the study.
- DPM and LMC led the implementation of the study.
- **STW** curated and analyzed the data.
- EL reviewed the analysis.

- EL and DIP reviewed the concept.
- **STW** wrote the initial draft and led the writing of the manuscript.
- EL, DIP, JM, LMC, OMA, NSS, and DPM critically reviewed the draft.
- All authors have read and approved the final version of the manuscript

Paper III:

Wafula ST, Lorenz E, Musoke D, May J, Puradiredja DI, Lamshöft MM. Do wealth, education, and urbanicity promote timely healthcare-seeking and diagnostic testing for febrile children? A meta-analysis of 16 national surveys in sub-Saharan Africa. BMC Public Health. 2024

Contributions for paper III are as follows.

- **STW**, EL and DIP: Conceived the study.
- **STW**: Curated and analysed data and initiated manuscript writing.
- EL Reviewed the analysis.
- EL, JM, MML, DM and DIP: Provided a critical review of the manuscript.
- All authors read and approved the manuscript.

9.0 Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: ....

10.0 Acknowledgements

I would like to acknowledge and thank my supervisors, Dr Eva Lorenz, Dr. Ismajani Puradiredja, and Professor Jürgen May. I am deeply grateful to Eva for her timely and insightful guidance on the depth and direction of my research. Her stimulating, encouraging conversations along with unwavering professional integrity pushed me to deliver high quality research. I am also thankful to Dr. Puradiredja for her unwavering support and commitment to shaping my research, especially in areas requiring her expertise such as aspects surveys and healthcare-seeking behaviours. I also applaud the many interesting discussions with primary supervisor, Prof. May, where he challenged me to consider alternate perspectives and explore additional research questions. I appreciate his belief in me and his willingness to make time for discussions despite his busy schedule.

My thanks also go to members of my thesis committee; Prof Heiko Becher, Prof. Olaf von dem Knesebeck for their insightful and thought-provoking questions, which helped shape my work. Their time, expertise, and encouragement helped me improve the quality of my research.

I am indebted to many colleagues at Bernard Nocht institute, particularly, Dr Johanna Brinkel, for supportive conversations and guidance on systematic reviews, and interpretation. Thanks to Dr Ralf KrumKamp for guidance with some statistical analyses and to Ulrike Kolander and Linda Dvorak for excellent administrative support. I would also like to appreciate Dr. Lauren Cohee at the University of Liverpool for her great insights and support with data acquisition for one of the PhD studies. I also appreciate my co-authors, Maike Lamshöft, David Musoke, Nicole Struck, Theresa Habermann, Anna Mara Franke, Don Mathanga and Oumou Maiga-Ascofare, for incredible insights on the publications.

Thanks to all my family and friends for their constant support. Special thanks to my dad David Mabonga for instilling a love of reading in me from a young age and for always encouraging me to dream higher. To my wife, Pamela and my son, Asher, this thesis would not have been possible without your love, kindness and patience.

Lastly, I thank the Almighty God for the good health, peace and love throughout the PhD journey. This achievement would not have been possible without his blessings.