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Exploring the protective effects of thalassemia against malaria in Africa: a systematic review

Augustine Boakye Donkor[1,2,3], Samuel Badu Nyarko[4], Kwame Kumi Asare[5], Cecil Kwame Mfum Asa-Atiemo[6], Kwadwo Asamoah Kusi[6], Yaw Asare Afrane[3] and Linda Eva Amoah[6*]

Abstract

Introduction Thalassemia, a hereditary blood disorder characterized by abnormal hemoglobin production, is prevalent in malaria-endemic regions, particularly among individuals of African descent. This hemoglobinopathy is believed to confer protection against malaria, reducing the severity of the disease and its associated complications. This systematic review and meta-analysis aimed to evaluate the protective effects of thalassemia against malaria, drawing insights from studies conducted in Africa between 2013 and 2025.

Methods This review adhered to the PRISMA guidelines and has been registered on PROSPERO. A comprehensive literature search was conducted via PubMed, Scopus, Cochrane Library, Embase and Google Scholar, supplemented by manual reference checks. Boolean search terms such as "thalassemia," "malaria," and "Africa" were used. The meta-analysis was conducted via R version 4.4.1, and a random effects model was used to calculate pooled odds ratios (ORs). Heterogeneity was assessed via the I2 statistic, and publication bias was evaluated via funnel plots and Egger's test.

Results Among the 4,957 screened articles, 15 studies met the inclusion criteria, with eight providing sufficient data for meta-analysis. The meta-analysis indicated that thalassemic individuals had lower odds (OR: 0.856) of developing malaria than non-thalassemic individuals. Mechanistically, alpha thalassemia has been shown to reduce cytoadhesion and rosette formation and enhance immune clearance, with favorable interactions observed with the haptoglobin phenotype (Hp2-1).

Conclusion Although the pooled estimate suggested a protective trend, the association was not statistically significant and was characterized by substantial heterogeneity across studies. While these findings underscore the evolutionary link between hemoglobinopathies and malaria resistance, further research is needed to elucidate molecular pathways and broader implications of thalassemia.

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Keywords Thalassemia, Malaria, Hemoglobin, Protection, Genetics, Hemoglobinopathy

*Correspondence:
Linda Eva Amoah
levaamoah@noguchi.ug.edu.gh
Full list of author information is available at the end of the article

Introduction

Microbial infections and genetic disorders in Africa contribute significantly to high morbidity and mortality rates in the region and are exacerbated by limited access to healthcare [1]. Historically, these challenges have lowered life expectancy in Africa compared with industrialized nations [2, 3]. Africa, the origin of several hemoglobinopathies, has experienced a profound public health impact from hereditary disorders, such as thalassemia, which confers protection against malaria [4].

Malaria remains a major cause of illness and death in Africa, particularly affecting children under five years of age and pregnant women [5]. It is caused mainly by *Plasmodium* in human and animal hosts. In 2023, the reported incidence of malaria was 60.4 cases per 1000 people at risk, over 90% of whom were in Africa. The high prevalence of malaria has influenced human host genetic factors, such as sickle cell trait and thalassemia [6], which have provided survival advantages in malaria-endemic areas [7]. Thalassemia, including alpha and beta forms, alters hemoglobin structures, potentially disrupting the lifecycle of *Plasmodium falciparum*, the deadliest human malaria parasite species [8]. Discovered in the mid-twentieth century, research has consistently shown that individuals with thalassemia experience a reduced incidence of severe malaria [9, 10]. However, the specific mechanisms underlying this protective effect remain an active area of investigation.

Thalassemias are a group of genetic blood disorders that affect one or more of the four [4] hemoglobin chains, modifying the production and function of hemoglobin. There are two forms of thalassemia disorders, alpha-thalassemia, and beta-thalassemia, depending on which hemoglobin chain is affected. Like sickle cell anemia, heterozygous alpha- or beta-thalassemia presents with mild thalassemic maladies and confers partial malaria protection on the host [11]. Thalassemia is common in Africa and Asia, where malaria endemicity occurs, suggesting a coevolutionary adaptation of host genetics with parasite-disease burden [12, 13]. Thalassemia may protect against malaria through several biological mechanisms. On the genetic level, the reduced expression of complement receptor 1 (CR1) proteins in thalassemic individuals diminishes rosetting and splenic clearance of [14, 15]. On the molecular and immunological arms, thalassemia protects against malaria through increased phagocytosis of infected cells, hemolysis and heme accumulation, oxidative damage and increased affinity for antibodies [14, 16, 17]. Additionally, genetic interactions with haptoglobin genotypes (e.g., Hp2-1) [18, 19] amplify this protective effect by improving immune responses and reducing oxidative damage. Positive epistatic protection has also been reported for alpha- and beta-thalassemias. However, these benefits may vary with other genetic traits, such as Hp2-2 and sickle cell traits [20].

The prevalence of thalassemia in Africa aligns with high malaria transmission, particularly in West and East Africa [18, 21]. This genetic epidemiological association of malaria and thalassemia over time highlights the selective pressure that has maintained high frequencies of thalassemia in certain regions [22]. Environmental factors, such as mosquito-breeding climates, intensify the interaction between genetics and malaria resistance [23–25]. Despite significant research, gaps remain in understanding the role of thalassemia, epistatic interactions, and specific protective mechanisms against malaria. With many studies conducted across Africa, this systematic review and meta-analysis comprehensively assessed the protective influence of thalassemia against malaria in African populations, exploring genetic and molecular mechanisms and public health implications of their unique interplay.

Methodology

Search strategy

The study has been registered on PROSPERO with registration number PROSPERO 2026 CRD420261294712. This study was designed following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [26] to ensure transparency and replicability in the review process. We conducted a comprehensive literature search covering the period between 2013 and 2025, utilizing key electronic databases: PubMed, Scopus, Cochrane Library, Embase and Google Scholar. Search strategies was adapted for each database. Studies on Thalassemia or other hemoglobinopathies, malaria, and immunity or resistance to malaria were found using controlled vocabulary (Emtree and MeSH) and free-text terms Embase and Cochrane Library. Regional and national-level terms were used to limit searches to African contexts. When possible, proximity operators were used to increase accuracy in Scopus. When appropriate, searches were restricted to human studies; English was the language of interest and search was restricted to 2013–2025.

For PubMed, the following Boolean search terms were used:

(Thalassaemia OR thalassemic OR haemoglobinopathy OR hemoglobinopathy OR Hemoglobin variants) AND Malaria (Resistance OR Immunity) AND (Africa OR West Africa OR North Africa OR East Africa OR South Africa OR Sub-Saharan Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cabo Verde OR Cameroon OR Central African Republic OR Chad OR Comoros OR Congo OR Cote d'Ivoire OR Democratic Republic of the Congo OR Djibouti OR

Egypt OR Equatorial Guinea OR Eritrea OR Eswatini OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria 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 Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe).

The search was supplemented by manually screening the reference lists of relevant articles to ensure that no important studies were overlooked.

Inclusion and exclusion criteria

The inclusion criteria were set to minimize selection bias. Studies were included if they met the following conditions:

1) The study population consisted of thalassemic patients who were diagnosed with malaria.
2) Studies provided data on the relationship between thalassemia and malaria protection and reported relevant outcomes (such as malaria infection rates or severity of malaria).
3) Articles were published in peer-reviewed journals between 2013 and 2025.
4) Observational studies (case–control, cohort, cross-sectional), randomized control trials, clinical trials, and clinical studies.

The following exclusion criteria were applied:

1) Articles published in languages other than English.
2) Studies focusing on hemoglobinopathies other than thalassemia (e.g., sickle cell disease).
3) Review articles, letters to the editor, case reports, and studies lacking sufficient primary data for meta-analysis.

Data extraction

Two independent abstractors extracted the data via a standardized form to ensure consistency. The extracted details included the following:

1) Study characteristics: Author(s), publication year, journal, title, and abstract source (database).
2) Study design and setting: The study design, country(ies)/region(s), sex and age distribution of participants, intervention/policy descriptions, and how thalassemia and malaria were diagnosed.
3) Outcomes: Outcomes, such as malaria infection rates, disease severity, and thalassemia variant(s), were determined.

For the studies included in the meta-analysis, we extracted odds ratios (ORs), 95% confidence intervals (CIs) and their p values, as well as the distributions of thalassemia variants and malaria phenotypes with significant heterogeneity.

To further explore the cause of heterogeneity, a Q statistic for explained residual heterogeneity (QE) and a Q statistic for Moderators (QM)-omnibus test for moderators were performed. These tests helped to identify whether study-level factors explained the variability between studies. A funnel plot was constructed to visually assess publication bias, and Egger's test was applied to statistically evaluate the symmetry of the funnel plot, with a symmetric funnel plot indicating no significant publication bias.

Results

Study inclusion

The initial search across PubMed, Scopus, Cochrane Library, Embase and Google Scholar identified 4,957 articles Study search was done in January 2025 and a follow search was done in 2026. After 1,644 duplicates were removed, 3,313 unique articles remained. Among these, 1,154 articles were excluded because they did not focus on studies conducted in Africa, leaving 2,159 articles. Further screening excluded 1,857 articles that did not align with the review scope, such as those not investigating the protective effects of thalassemia against malaria.

This narrowed the selection to 302 full-text articles, which underwent detailed evaluation. Of these, 290 were excluded for the following reasons: non-English publications (n = 11), inaccessible articles (n = 23), studies not reporting the expected outcomes (n = 223), and irrelevant study types, including reviews, letters, and case reports (n = 33). Ultimately, 15 articles were selected for data extraction, with 8 included in the meta-analysis. Figure 1 provides a detailed breakdown of the article selection process using a Cochrane flow diagram.

Study selection

All retrieved records were imported into Rayyan and duplicates were removed. Two reviewers (ABD and SBN) independently screened titles and abstracts for eligibility. Full texts of potentially relevant articles were assessed independently against the inclusion criteria. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

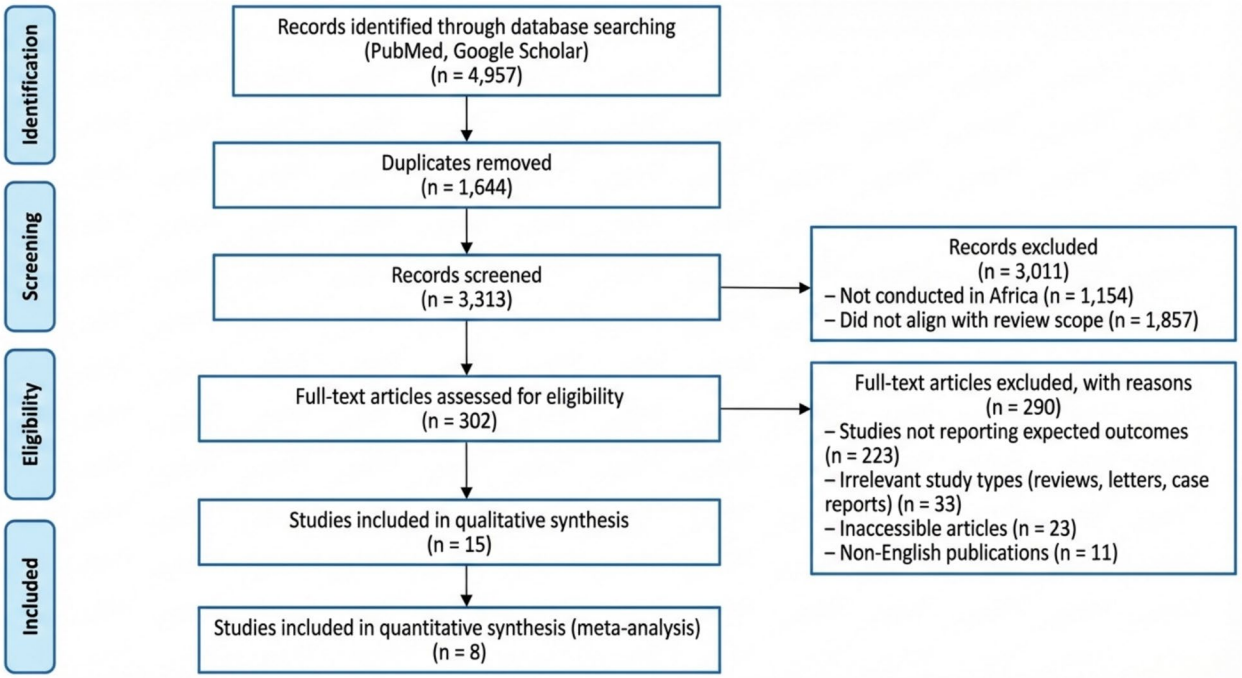

Fig. 1 Cochrane flow diagram of article selection for the review and meta-analysis.

Study characteristics

The systematic review identified 15 studies that met the inclusion criteria and were published between 2013 and 2025. Seven studies were published from 2013–2017, and the remaining six were published from 2018–2024. The sample sizes across the studies ranged from 128 to 2,240 participants. Of these, 10 studies focused on children aged 1 month to 14 years, 1 study targeted adults, and 4 included a mixed population of children and adults.

Most studies included both male and female participants, with their geographic distribution spanning several African countries. Kenya accounted for the greatest number of studies (n = 6), followed by Ghana (4), Tanzania (n = 2), Uganda (n = 2), and one study from Malawi (Table 1).

The primary objective of these studies was to explore the relationship between α-thalassemia and malaria, with a focus on the genetic and biological mechanisms through which thalassemia offers protection against malaria. All studies diagnosed thalassemia through polymerase chain reaction (PCR), whereas malaria diagnosis was predominantly performed via parasite enumeration via microscopy. Among the 15 studies, 8 concluded that α-thalassemia confers a protective effect against malaria.

Risk of bias assessment

The methodological quality of included studies was assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) for observational studies. The tool evaluates selection, comparability, and outcome/exposure domains. Studies were classified as low, moderate, or high risk of bias. Disagreements were resolved by discussion.

Meta-analysis

Eight of the 15 studies provided data suitable for inclusion in the meta-analysis, with a focus on the protective effect of thalassemia against malaria (Table 2).

Data synthesis

Meta-analysis was conducted using a random-effects model to account for between-study variability. Heterogeneity was assessed using Cochran's *Q* and the *I*2 statistic. *I*2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. Subgroup analyses were planned based on malaria phenotype (severe malaria vs parasitaemia). Sensitivity analysis was performed by sequentially removing individual studies.

Odds ratios (ORs) and their corresponding confidence intervals were extracted, log-transformed, and analyzed via forest and funnel plots. The random-effects model produced a pooled log OR of −0.156 (−0.44 − 0.128). When back-transformed (e^ − 0.20), this resulted in an estimated OR of 0.856, suggesting a protective effect of thalassemia against malaria.

Table 1 Summary of the characteristics of the studies included in the meta-analysis (n = 12)

Study Characteristics	Number of studies
Publication Date	
2013–2017	7
2018–2024	8
Population type	
Children	10
Adult	1
Mixed	4
Gender	
Male	0
Female	1
Both	14
Country of Studies	
Tanzania	2
Kenya	6
Uganda	2
Ghana	4
Malawi	1
Thalassemia Variant determined	
α-thalassemia	15
β-thalassemia	0
Method for malaria diagnosis	
Microscopy	8
RDT	2
PCR	2
Flow cytometry	2
Unspecified	1
Method of thalassemia diagnosis	
PCR	15

Abbreviations: RDT: Rapid diagnostic test; PCR: Polymerase chain reaction

However, the Q test for heterogeneity indicated a significant level of variability among the studies (Q (df = 7) = 40.66, $p = 0.000$), supported by an $I2$ value of 82.8%, reflecting substantial heterogeneity (Table 3). To identify potential sources of this variability, a subgroup analysis was performed. The QE test for residual heterogeneity revealed that variability remained significant even after considering moderators (QE (df = 7) = 40.26, $p = 0.000$). The QM omnibus test showed that the moderator itself significantly explains the heterogeneity (QM (df = 4) = 24.79, $p = 0.000$).

Heterogeneity analysis results

Possible contributors to the observed heterogeneity may include differences in study design, variations in the timing and methodologies employed, and environmental or geographical factors across the studies.

The forest plot summarizes the relationship between thalassemia and malaria protection based on eight distinct studies (Fig. 2). The x-axis represents the log odds ratio, where negative values suggest that thalassemia serves as a protective factor against malaria, whereas positive values indicate the opposite. The overall summary estimate shows a log odds ratio of 0.85 (0.79–0.91), suggesting a slight, though not statistically significant, protective effect of thalassemia against malaria.

A funnel plot was constructed to assess potential selection bias. Visually, the distribution of studies appeared symmetrical, suggesting that there was no evidence of bias. To further evaluate funnel plot symmetry, Egger's test was performed, yielding a t statistic of −0.1103 (df = 4, p = 0.9175). These results indicate that there is no significant publication bias (Fig. 3). Because fewer than ten studies were included in the meta-analysis, funnel-plot interpretation is limited and publication bias could not be reliably assessed, in line with Cochrane recommendations.

Table 2 Summary of studies reporting the protective effect of α-thalassemia on malaria

Study	Thalassemia variants	OR (95%CI)	p value	Main results
Saguti et al., 2013[27]	α-/α-, α-/αα	0.81(0.45–1.48)	0.5	has a protective effect on severe malaria
Mpimbaza et al., 2018 [28]	α-/α-	0.34 (0.16–0.73)	0.005	"α-/α-" has a protective effect on severe malaria
Kariuki et al., 2023[24]	α-/α-, α-/αα	0.91 (0.46–1.73)	0.766	α-thalassemia has no protective effect on severe malaria
Atkinson et al., 2014 [18]	α-/α-	0.69 (0.55–091)	0.08	"α-/α-" has a protective effect on severe malaria
Daou et al., 2015 [29]	α-/α-, α-/αα	1.83 (1.07–3.42)	0.027	α-thalassemia has a higher prevalence of anti-malaria antigen
Lamptey et al., 2019 [31]	α-/α-, α-/αα	0.52(0.28–0.97)	0.037	Heterozygous α-thalassaemia trait had reduced risk of asexual parasite carriage. There was however, no association between α-thalassaemia trait and risk of gametocyte carriage
Opi et al., 2018 [23]	α-/α-, α-/αα	0.98 (0.82–1.18)	0.0001	Modified risk of malaria protection
Ndila et al., 2018[30]	α-/α-, α-/αα	0.83 (0.76–0.90)	0.0002	α-thalassemia has no protective effect on malaria parasitemia

Abbreviations: α-/α-: homozygous alpha thalassemia, α-/αα: heterozygous alpha thalassemia, OR: odds ratio, 95% CI: confidence interval

Table 3 Heterogeneity measures from meta-analysis

Measure	Value	95% CI/df	p-value
Cochran's Q	40.66	df = 7	0.000
H statistic	2.410	1.677–3.098	
I2 (%)	82.8%	64.4% – 89.6%	

Discussion

The relationship between thalassemia and malaria represents a fascinating example of host genetic adaptation in response to selective pressure from a parasitic burden [30]. The pooled estimate suggested a possible protective effect of α-thalassemia against malaria and was accompanied by substantial heterogeneity (I2 = 82.8%). These findings should therefore be interpreted cautiously. This protective effect aligns with the evolutionary hypothesis that certain malaria protection-associated host genetic traits such as α-thalassemia, persist in regions, especially Africa, where malaria imposes strong selective pressure.

A protective role for α-thalassemia is supported by the direction of the pooled effect estimate. However, the significant heterogeneity among the included studies ($I^2 = 82.8\%$, $p < 0.001$) necessitates caution in the interpretation. As seen in the forest plot (Fig. 2), this high degree of variability suggests that the strength and, in certain situations, the direction of the reported association vary considerably between studies. For example, a number of studies like Mpimbaza et al., 2018; Atkinson et al., 2014) found a near-null effect (OR = 0.98), while others, such as Daou et al. (2015), indicated an elevated risk (OR = 1.83). Others, however, observed robust protective effects (OR < 0.70). This variation highlights the fact that the link is not consistent and is probably influenced by additional variables.

The distinction between homozygous and heterozygous α-thalassemia is pivotal for understanding the protective mechanisms at play. While both genetic forms reduce malaria severity, they differ biologically [13, 17, 19, 23]. Heterozygous α-thalassemia, involving a single α-globin gene deletion, is more prevalent in the studied

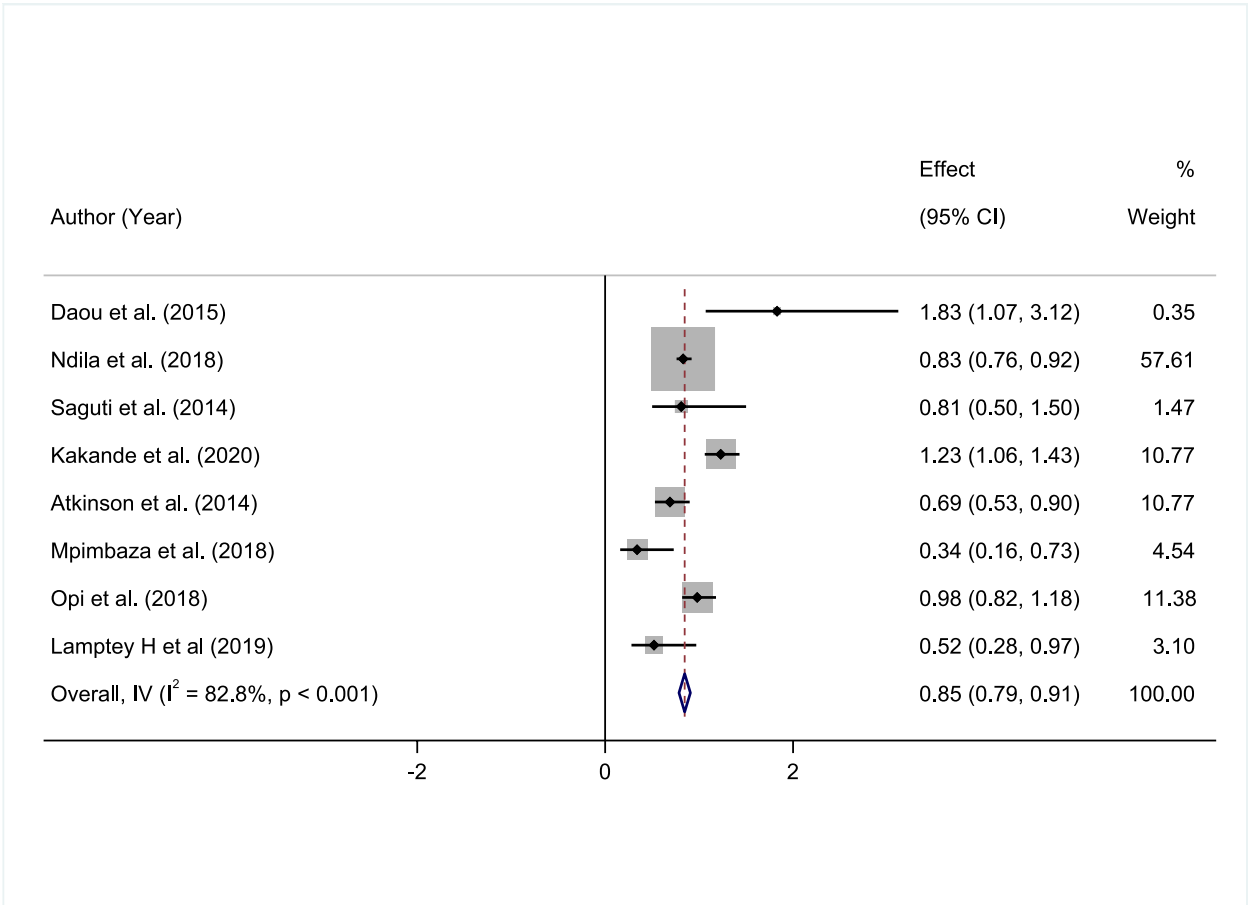

Fig. 2 A forest plot showing that thalassemia effect on malaria patients compared with normal individuals

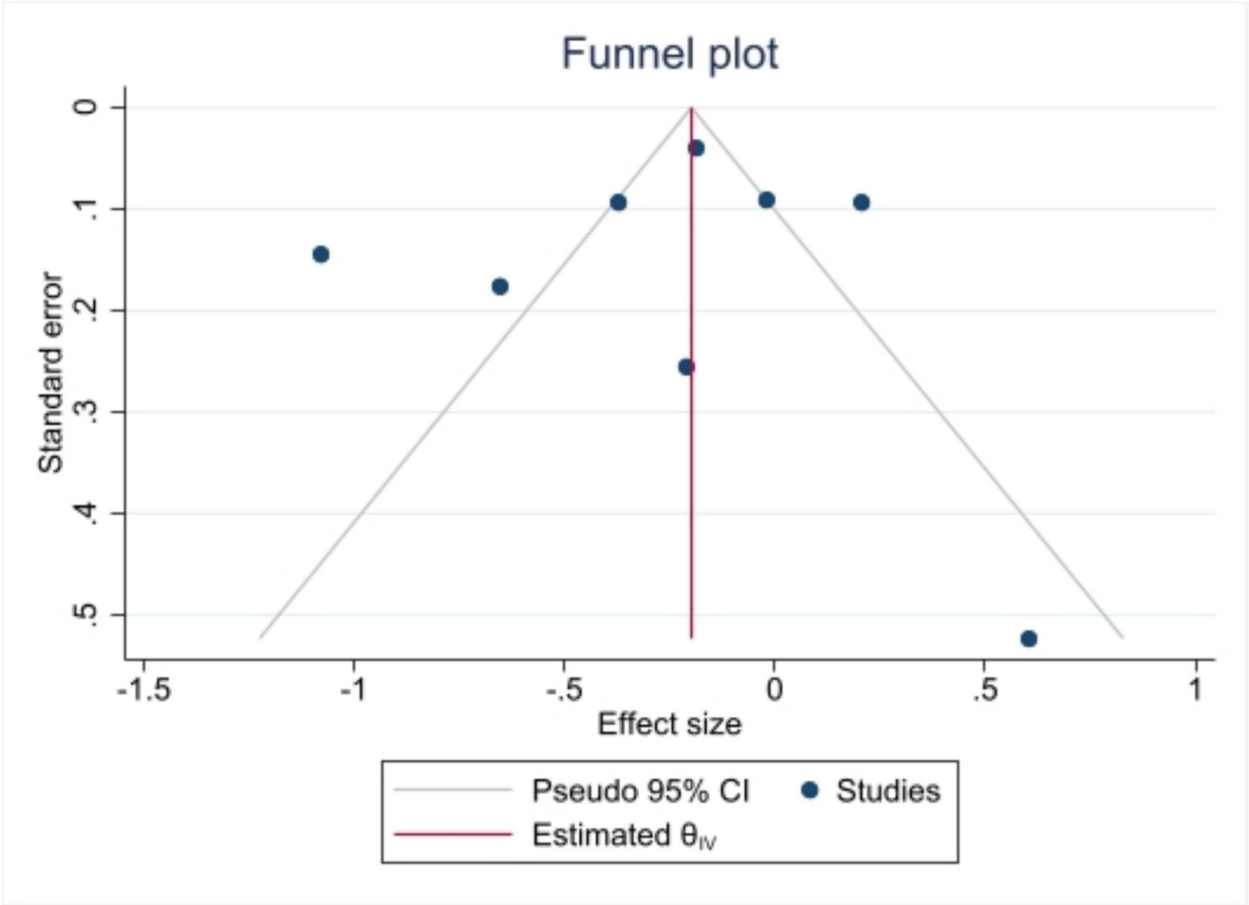

Fig. 3 A funnel plot showing the absence of publication bias due to its symmetrical nature

populations and provides protection by preventing the gradual decline in hemoglobin [17]. This is likely because of microcytosis (smaller-than-normal red blood cells) and an increased RBC count that hinders the ability of *Plasmodium falciparum* to thrive [33]. However, despite this protective effect, heterozygous individuals have a greater parasite prevalence than do those with homozygous α-thalassemia, highlighting that while they are less likely to develop severe malaria complications, they are still susceptible to uncomplicated infections [12, 19]. Conversely, homozygous α-thalassemia, involving deletions of both α-globin genes, may confer more robust immune protection, potentially through enhanced immune responses or more effective clearance of parasitized red blood cells [27]. These findings indicate that, while both forms offer protection, the biological mechanisms differ, warranting further research to elucidate these pathways.

The protective effects of α-thalassemia against malaria can be explained by several genetic and molecular mechanisms. A central mechanism is the reduction of cytoadhesion and rosette formation, processes that are critical for *Plasmodium falciparum* to evade immune detection and establish severe disease [4, 27]. In individuals with α-thalassemia, parasitized red blood cells exhibit a decreased ability to adhere to endothelial cells, impairing their ability to contribute to severe clinical complications [27, 28]. Additionally, hemichromes, which form in thalassemic red blood cells, induce oxidative stress and reduce the expression of PfEMP1, a key molecule facilitating cytoadhesion [4, 27, 34]. This weakens the parasite's ability to evade the immune system, contributing to reduced disease severity. Furthermore, enhanced immune clearance represents another key mechanism; thalassemic red blood cells are more susceptible to opsonization by immunoglobulin G (IgG) and complement proteins, promoting their removal by phagocytes such as macrophages [29]. This immune mechanism interrupts parasite replication and prevents progression to severe disease.

Importantly, gene interactions, particularly epistasis, modulate the malaria protection conferred by

α-thalassemia. The interaction between α-thalassemia and haptoglobin (Hp) genotypes shows positive epistasis, as the coinheritance of α-thalassemia and the Hp2-1 genotype enhances protection by improving oxidative stress regulation [9, 13]. Conversely, the coinheritance of α-thalassemia and HbAS (sickle cell trait) results in negative epistasis, reducing the protective effects by altering red blood cell characteristics such as cytoadhesion and PfEMP1 expression [15, 18]. These findings emphasize the complex genetic interplay that influences protection, suggesting that population-specific genetic factors must be accounted for in understanding malaria risk and designing interventions.

From a public health perspective, these findings carry critical implications. Understanding the protective effects of α-thalassemia opens avenues for targeted interventions, such as therapies that mimic its protective biological mechanisms. Strategies that reduce cytoadhesion, increase immune clearance, or modulate oxidative stress could prove beneficial for non-thalassemic populations at risk of *Plasmodium* infections. However, individuals with α-thalassemia are not entirely immune to malaria. While they are less likely to experience severe complications, they can still harbor *Plasmodium* parasites, particularly in uncomplicated infections [12, 27]. This highlights the need for continued reliance on standard malaria prevention strategies, including the use of insecticide-treated bed nets and antimalarial prophylaxis [12, 18].

Limitations of the review

This study is subject to several limitations that must be considered when the findings are interpreted. First, significant heterogeneity was observed among the included studies ($I2 = 81.25\%$), likely because of differences in study design, population characteristics, and malaria transmission intensity in various regions. This variability makes it challenging to generalize the results to all malaria-endemic areas. Additionally, many studies have not consistently differentiated between homozygous and heterozygous α-thalassemia, limiting the ability to assess their distinct contributions to malaria protection. Studies of beta-thalassemia are scarce in the literature pool and are absent in this study.

Another limitation is the reliance on observational studies, which are prone to confounding factors, such as coexisting genetic traits (e.g., sickle cell traits or G6PD deficiency), and environmental influences, such as coinfections and vector control interventions. These factors may have influenced the reported protective effects of α-thalassemia. Moreover, variations in the diagnostic criteria for malaria and thalassemia across studies may have introduced bias, affecting the accuracy and comparability of the results.

Finally, most of the reviewed studies were conducted in specific geographic regions, which may not fully represent the global diversity of malaria-endemic settings. Future research addressing these limitations will be critical to refining our understanding of the relationship between α-thalassemia and malaria.

Future research directions

The relationship between α-thalassemia and malaria presents a unique opportunity to explore the intricate interplay of genetic and other biological factors in host resistance against infectious diseases. Future research should prioritize distinguishing the protective effects of homozygous and heterozygous α-thalassemia, including their respective mechanisms and clinical outcomes. Future investigations into the precise molecular and cellular pathways underlying thalassemia- related malaria protection is essential. Additionally, exploring epistatic interactions between α-thalassemia and other genetic traits, such as sickle cell or G6PD deficiency, as well as different environmental contexts, will provide crucial insights into the context-dependent nature of malaria protection. Large, population-specific studies in diverse malaria-endemic regions are needed to account for variations in host and parasite genetic diversity. Furthermore, longitudinal cohort studies and experimental models could provide a deeper understanding of how α-thalassemia influences malaria susceptibility over time and across life stages. Finally, evaluating the public health implications of this genetic trait in malaria-endemic regions will help in the management of both infectious and genetic diseases in light of its evident benefits.

Conclusion

In conclusion, the findings from our systematic review and meta-analysis showed that while α-thalassemia significantly reduces malaria severity, it does not eliminate the risk of infection. The genetic and biological mechanisms underlying this protection, including impaired parasite cytoadhesion, immune clearance, and oxidative stress modulation, provide a complex, multifaceted defense for hosts. These mechanisms, combined with the evolutionary perspective of gene–environment interactions, highlight the importance of integrating genetic insights into malaria control strategies. Future research should focus on exploring gene interactions in diverse populations and clarifying the distinct biological pathways contributing to malaria protection by α-thalassemia.

Abbreviations

α-thal	Alpha thalassemia
β-thal	Beta thalassemia
CI	Confidence interval

CR1	Complement receptor 1
G6PD	Glucose-6-phosphate dehydrogenase
Hb	Hemoglobin
Hp2.2	Haptoglobin phenotype 2.2
Hp2-1	Haptoglobin phenotype 2.1
OR	Odds ratio
Pf	*Plasmodium falciparum*
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBC	Red blood cell

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Authors' contribution
ABD developed the study protocol in collaboration with SBN. SBN and ABD performed the data analysis. KKA, CKMAA, KAK and LEA reviewed the manuscript. ABD, SBN, KKA, CKMAA, KAK, LEA, and YA formulated the draft search strategy. All authors read and approved the final manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]West African Genetic Medical Centre, University of Ghana, Accra, Ghana. [2]Department of Clinical Microbiology, Cape Coast Teaching Hospital, Cape Coast, Ghana. [3]Department of Medical Microbiology, Medical School, University of Ghana, University of Ghana, Accra, Ghana. [4]Department of Medical Biochemistry, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana. [5]Biomedical and Clinical Research Centre, College of Allied Health Sciences, University of Cape Coast, Cape Coast, Ghana. [6]Department of Immunology, Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana.

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References

1. Lin GL, McGinley JP, Drysdale SB, Pollard AJ. Epidemiology and immune pathogenesis of viral sepsis. Front Immunol. 2018. https://doi.org/10.3389/fimmu.2018.02147.
2. Twum S, Fosu K, Felder RA, Sarpong KAN. Bridging the gaps in newborn screening programmes: Challenges and opportunities to detect haemoglobinopathies in Africa. Vol. 12, African Journal of Laboratory Medicine. 2023.
3. Guisan MC, & EP. aeid1627. Applied Econometrics and International Development. 2006;Vol. 16–2.
4. McGann PT, Williams AM, Ellis G, McElhinney KE, Romano L, Woodall J, et al. Prevalence of inherited blood disorders and associations with malaria and anemia in Malawian children. Blood Adv. 2018. https://doi.org/10.1182/bloodadvances.2018023069.
5. Grant AV, Roussilhon C, Paul R, Sakuntabhai A. The genetic control of immunity to *Plasmodium* infection. BMC Immunol. 2015. https://doi.org/10.1186/s12865-015-0078-z.
6. Withrock IC, Anderson SJ, Jefferson MA, McCormack GR, Mlynarczyk GSA, Nakama A, et al. Genetic diseases conferring resistance to infectious diseases. Genes Dis. 2015. https://doi.org/10.1016/j.gendis.2015.02.008.
7. Rao E, Kumar Chandraker S, Misha Singh M, Kumar R. Global distribution of β-thalassemia mutations: an update. Gene. 2024. https://doi.org/10.1016/j.gene.2023.148022.
8. Akide-Ndunge OB, Ayi K, Arese P. The Haldane malaria hypothesis: facts, artifacts, and a prophecy. Redox Rep. 2003. https://doi.org/10.1179/135100003225002952.
9. Goheen MM, Campino S, Cerami C. The role of the red blood cell in host defence against falciparum malaria: an expanding repertoire of evolutionary alterations. Br J Haematol. 2017. https://doi.org/10.1111/bjh.14886.
10. Ebel ER, Kuypers FA, Lin C, Petrov DA, Egan ES. Common host variation drives malaria parasite fitness in healthy human red cells. Elife. 2021. https://doi.org/10.7554/eLife.69808.
11. Kamanzi NG. Hemoglobinopathy for Malaria Protection: A Comprehensive Review. Idosr Journal Of Biochemistry, Biotechnology And Allied Fields. 2024;9(3):30–4. Available from: https://www.idosr.org/hemoglobinopathy-for-malaria-protection-a-comprehensive-review/ Accessed 13th January 2024.
12. Angastiniotis M, Lobitz S. Thalassemias: an overview. Int J Neonatal Screen. 2019. https://doi.org/10.3390/ijns5010016.
13. Penglong T, Saensuwanna A, Jantapaso H, Phuwakanjana P, Jearawiriyapaisarn N, Paiboonsukwong K, et al. MiR-214 aggravates oxidative stress in thalassemic erythroid cells by targeting ATF4. PLoS ONE. 2024;19(4 April):1.
14. Dhangadamajhi G, Kar SK, Ranjit M. The survival strategies of malaria parasite in the red blood cell and host cell polymorphisms. Malar Res Treat. 2010. https://doi.org/10.4061/2010/973094.
15. Ayi K, Turrini F, Piga A, Arese P. Enhanced phagocytosis of ring-parasitized mutant erythrocytes: A common mechanism that may explain protection against falciparum malaria in sickle trait and beta-thalassemia trait. Blood. 2004;104(10):3364–71.
16. Opoku-Okrah C, Gordge M, Kweku Nakua E, Abgenyega T, Parry M, Robertson C, et al. An investigation of the protective effect of alpha+-thalassaemia against severe Plasmodium falciparum amongst children in Kumasi, Ghana. Int J Lab Hematol. 2014. https://doi.org/10.1111/ijlh.12122.
17. Eridani S. Sickle cell protection from malaria. Vol. 3, Hematology Reports. MDPI; 2011. p. 72–7.
18. Atkinson SH, Uyoga SM, Nyatichi E, Macharia AW, Nyutu G, Ndila C, et al. Epistasis between the haptoglobin common variant and α +thalassemia influences risk of severe malaria in Kenyan children. Blood. 2014. https://doi.org/10.1182/blood-2013-10-533489.
19. Destro-Bisol G, Giardina B, Sansonetti B, Spedini G. Interaction between oxidized hemoglobin and the cell membrane: a common basis for severalfalciparum malaria-linked genetic traits. Am J Phys Anthropol. 1996;101(S23):137–59.
20. Ha J, Martinson R, Iwamoto SK, Nishi A. Hemoglobin E, malaria and natural selection. Evol Med Public Health. 2019;2019(1):232–41.
21. Krause MA, Diakite SAS, Lopera-Mesa TM, Amaratunga C, Arie T, Traore K, et al. α-thalassemia impairs the cytoadherence of plasmodium falciparum-infected erythrocytes. PLoS ONE. 2012. https://doi.org/10.1371/journal.pone.0037214.
22. Flint J, Harding RM, Boyce AJ, Clegg JB. The population genetics of the haemoglobinopathies. Baillieres Clin Haematol. 1998;11(1):1–51.
23. Opi DH, Swann O, Macharia A, Uyoga S, Band G, Ndila CM, et al. Two complement receptor one alleles have opposing associations with cerebral malaria and interact with α+thalassaemia. Elife. 2018. https://doi.org/10.7554/eLife.31579.
24. Kariuki SN, Macharia AW, Makale J, Nyamu W, Hoffman SL, Kapulu MC, et al. The Dantu blood group prevents parasite growth in vivo: evidence from a controlled human malaria infection study. Elife. 2023. https://doi.org/10.7554/eLife.83874.
25. Kakande E, Greenhouse B, Bajunirwe F, Drakeley C, Nankabirwa JI, Walakira A, et al. Associations between red blood cell variants and malaria

among children and adults from three areas of Uganda: A prospective cohort study. Malar J. 2020. https://doi.org/10.1186/s12936-020-3105-3.
26. Page, Matthew J., Joanne E. McKenzie, Patrick M. Bossuyt, Isabelle Boutron, Tammy C. Hoffmann, Cynthia D. Mulrow, Larissa Shamseer et al. "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews." *bmj* 372 (2021).
27. Saguti F, Balthazary S, Manjurano A, Max R, Tenu F, Francis F, et al. Relationship between alpha+-thalassaemia and glutathione-S-transferases polymorphisms in children with severe malaria in Tanzania. Tanzan J Health Res. 2013;15(2).
28. Mpimbaza A, Walakira A, Ndeezi G, Katahoire A, Karamagi C, Nsobya SL, et al. Associations between erythrocyte polymorphisms and risks of uncomplicated and severe malaria in Ugandan children: A case control study. PLoS ONE. 2018. https://doi.org/10.1371/journal.pone.0203229.
29. Daou M, Kituma E, Kavishe R, Chilongola J, Mosha F, Van Der Ven A, et al. α-Thalassaemia trait is associated with antibody prevalence against malaria antigens AMA-1 and MSP-1. J Trop Pediatr. 2015. https://doi.org/10.1093/tropej/fmu077.
30. Lamptey H, Ofori MF, Adu B, Kusi KA, Dickson EK, Quakyi I, et al. Association between alpha-thalassaemia trait, *Plasmodium falciparum* asexual parasites and gametocyte carriage in a malaria endemic area in Southern Ghana. BMC Res Notes. 2019;12(1):134.
31. Lee WC, Russell B, Rénia L. Sticking for a cause: the *falciparum* malaria parasites cytoadherence paradigm. Front Immunol. 2019. https://doi.org/10.3389/fimmu.2019.01444.
32. Zareen S, Rehman HU, Gul N, Zareen H, Hisham M, Rehman MU, et al. Malaria is still a life threatening disease review. Journal of Entomology and Zoology Studies JEZS. 2016;105(45).
33. Scovino AM, Totino PRR, Morrot A. Eryptosis as a new insight in malaria pathogenesis. Front Immunol. 2022. https://doi.org/10.3389/fimmu.2022.855795.
34. Zhang S, Chen Z, Chen M, Huang H. Current status and trends in thalassemia burden across South, East and Southeast Asia, 1990–2021 a systematic analysis for the global burden of disease study 2021. BMC Public Health. 2024;24(1):3472. Available from: https://bmcpublichealth.biomedcentral.com/articles/https://doi.org/10.1186/s12889-024-20983-y Accessed 15th January, 2024.

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