THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Taylor SM, Parobek CM, Fairhurst RM. Haemoglobinopathies and the clinical epidemiology of malaria: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; published online March 23. DOI:10.1016/S1473-3099(12)70055-5.

Supplementary methods

Search Strategy

Our search of MEDLINE using PubMed (through September 9, 2011) used the search criteria: malaria [Title/Abstract] AND (thalassemia[Title/Abstract] OR hemoglobin[Title/Abstract] OR haemoglobin [Title/Abstract] OR sickle[Title/Abstract] OR erythrocyte[Title/Abstract] OR red blood cell[Title/Abstract]).

The Embase search (through September 9, 2011) used the search line: (malaria:ab OR malaria:ti) AND (thalassemia:ab OR thalassemia:ti OR hemoglobin:ab OR hemoglobin:ti OR OR haemoglobin:ab OR haemoglobin:ti OR sickle:ab OR sickle:ti OR erythrocyte:ab OR erythrocyte:ti OR (((red AND blood/exp AND cell:ab) OR red) AND blood/exp AND cell:ti)) AND [embase]/lim. For both searches, we limited the studies to those published in English and conducted in humans.

Outcome Assessment

The presence of *Plasmodium* parasites required demonstration by blood smear, rapid diagnostic test, or PCR testing. For inclusion, severe malaria needed to be defined as a positive test for *P. falciparum* parasitaemia combined with clinical criteria consonant with that defined by the WHO.[1] For the assessment of specific severe malaria syndromes, we required the description of standard definitions of severe malarial anaemia and/or cerebral malaria.[1] Uncomplicated malaria required *P. falciparum* parasitemia along with fever or another symptom suggestive of malaria and non-fulfillment of criteria for severe disease. Asymptomatic parasitaemia was defined as the presence of *P. falciparum* parasitaemia in cross-sectional surveys or the presence of *P. falciparum* parasitaemia in an otherwise asymptomatic patient from prospective or case-control studies. Vivax malaria was defined as the presence of *P. vivax* parasitaemia with fever or another symptom suggestive of malaria; non-malaria clinical syndromes were allowed to be defined on a study basis.

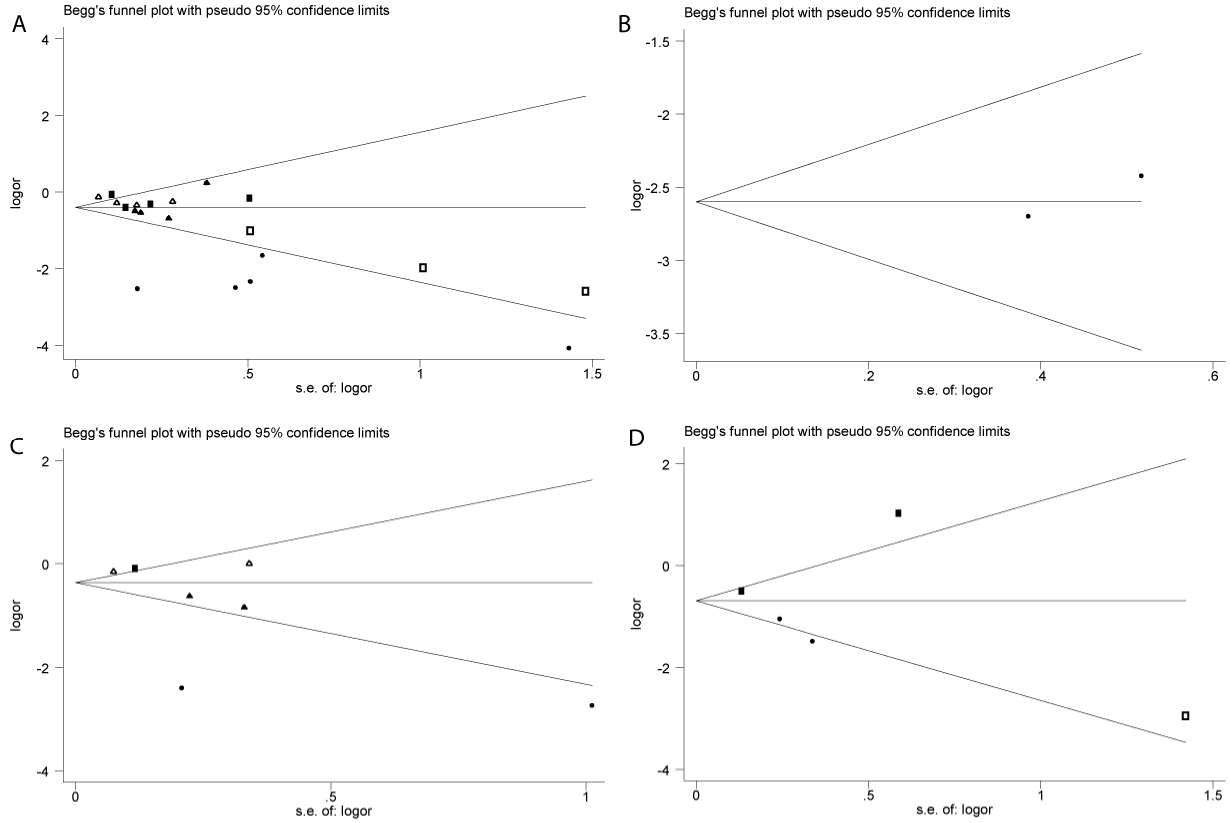
Assessment of Publication Bias

To assess for publication bias in the reporting of case-control studies that investigated haemoglobinopathies and malaria, funnel plots were constructed using metabias in Stata/IC (version 11, Stata Corp, College Station, TX). By Begg's test, the p-value for publication bias was 0·004 for all included studies that compared case patients to healthy controls.

When stratified by haemoglobinopathy, nonsignificant tests for bias were obtained for each hemoglobinopathy: HbAS (p = 0·697), HbCC (p = 0·174), HbAC (p = 0·652), homozygous α-thalassaemia (p = 0·358) and heterozygous α-thalassaemia (p = 0·573). When stratified by case syndrome, there was evidence of significant bias for studies of severe malaria (p = 0·009), but not for those of uncomplicated malaria (p = 1·00), cerebral malaria (p = 0·317), or severe malarial anaemia (p = 0·176) (Figure S1).

Because the clear differences in the estimates of protection from severe malaria between haemoglobinopathies suggested distinct biological correlates, we stratified the analysis by haemoglobinopathy. When studies of severe malaria were stratified by haemoglobinopathy, there was no evidence of significant publication bias upon testing of any of the individual variants: HbAS (p = 0·624), HbCC (p = 0·117), HbAC (p = 1·00), homozygous α-thalassaemia (p = 1·00) and heterozygous α-thalassaemia (p = 0·497). Though each of these stratified Begg's tests ultimately included few studies, taken together they suggest a lack of significant publication bias in the studies identified by our systematic review.

Figure S1. Funnel plots to assess publication bias in case-control studies of severe malaria (A), cerebral malaria (B), severe malarial anaemia (C), and uncomplicated malaria (D).



HbAS: filled circles; HbAC: filled squares; HbCC: open squares; homozygous α-thalassaemia: filled triangles; heterozygous α-thalassaemia: open triangles. To standardize methods, studies were included in bias assessment if they compared cases to healthy controls.

Table S1. PRISMA 2009 Checklist

Section/ topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	29-32, 34-35
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	29-32, 34-35
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 1, Fig 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 1, Fig 2, Table S2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9, Supplementary methods
Additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	27-34
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16-18, Panel 1
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8, Acknowledgements

Table S2. Summary and individual odds ratios from case-control studies estimating protection from malaria syndromes by haemoglobinopathies

Source	Cases	Controls	Odds Ratio (95% C. I.)	I^2 (p value)
Haemoglobin AS				
Hill et al (1991)[2]	Severe malaria	Severe non-malaria illness	0.09 (0.03 – 0.22)	NA
Hill et al (1991)[2]	Severe malaria	Uncomplicated malaria	0.39 (0.12 – 1.16)	37.15
Agarwal et al (2000)[3]	Severe malaria	Uncomplicated malaria	1.61 (0.28 – 6.18)	28.87
Modiano et al (2001)[4]	Severe malaria	Uncomplicated malaria	0.28 (0.07 – 0.85)	33.98
Summary[2-4]	*Severe malaria*	*Uncomplicated malaria*	*0.52 (0.20 – 1.38)*	*56.0% (0.103)*
Gilles et al (1967)[5]	Severe malaria	Healthy	0.19 (0.07 – 0.55)	NA
Modiano et al (2001)[4]	Severe malaria	Healthy	0.10 (0.04 – 0.26)	NA
Mockenhaupt et al (2004)[6]	Severe malaria	Healthy	0.02 (0 – 0.28)	NA
Ackerman et al (2005)[7]	Severe malaria	Healthy	0.08 (0.03 – 0.21)	NA
May et al (2007)[8]	Severe malaria	Healthy	0.08 (0.06 – 0.11)	NA
Jallow et al (2009)[9,a]	Severe malaria	Healthy	0.09 (0.05 – 0.16)	NA
Summary[4-8]	*Severe malaria*	*Healthy*	*0.09 (0.06 – 0.12)*	*17.6% (0.303)*
Ackerman et al (2005)[7]	Cerebral malaria	Healthy	0.09 (0.02 – 0.24)	NA
May et al (2007)[8]	Cerebral malaria	Healthy	0.07 (0.03 – 0.14)	NA
Jallow et al (2009)[9,a]	Cerebral malaria	Healthy	0.12 (0.07 – 0.21)	NA
Summary[7,8]	*Cerebral malaria*	*Healthy*	*0.07 (0.04 – 0.14)*	*0% (0.667)*
Ackerman et al (2005)[7]	Severe malarial anaemia	Healthy	0.06 (0.002 – 0.38)	NA
May et al (2007)[8]	Severe malarial anaemia	Healthy	0.09 (0.06 – 0.14)	NA
Jallow et al (2009)[9,a]	Severe malarial anaemia	Healthy	0.10 (0.04 – 0.24)	NA
Summary[7,8]	*Severe malarial anaemia*	*Healthy*	*0.09 (0.06 – 0.13)*	*0% (0.741)*
Willcox et al (1983)[10]	Uncomplicated malaria	Healthy	0.23 (0.10 – 0.44)	NA
Modiano et al (2001)[4]	Uncomplicated malaria	Healthy	0.35 (0.20 – 0.56)	NA
Summary[4,10]	*Uncomplicated malaria*	*Healthy*	*0.30 (0.20 – 0.45)*	*3.8% (0.308)*
Hill et al (1991)[2]	Uncomplicated malaria	Mild non-malaria illness	0.20 (0.09 – 0.39)	NA
Haemoglobin CC				
Agarwal et al (2000)[3]	Severe malaria	Uncomplicated malaria	0 (0 – 3.34)	NA
Modiano et al (2001)[4]	Severe malaria	Uncomplicated malaria	NA	NA
Summary[3,4]	*Severe malaria*	*Uncomplicated malaria*	*1.12 (0.12 – 10.70)*	*9.7% (0.293)*
Modiano et al (2001)[4]	Severe malaria	Healthy	0.14 (0.02 – 1.01)	NA
Mockenhaupt et al (2004)[6]	Severe malaria	Healthy	0.08 (0 – 1.38)	NA
May et al (2007)[8]	Severe malaria	Healthy	0.37 (0.14 – 0.99)	NA
Summary[4-6,8]	*Severe malaria*	*Healthy*	*0.27 (0.11 – 0.63)*	*0% (0.424)*
Modiano et al (2001)[4]	Uncomplicated malaria	Healthy	0 (0 – 0.41)	NA
Haemoglobin AC				
Guinet et al (1997)[11]	Severe malaria	Uncomplicated malaria	1.11 (0.33 – 4.31)	NA
Agarwal et al (2000)[3]	Severe malaria	Uncomplicated malaria	0.25 (0.05 – 0.80)	NA
Modiano et al (2001)[4]	Severe malaria	Uncomplicated malaria	1.12 (0.76 – 1.64)	NA
Summary[3,4,11]	*Severe malaria*	*Uncomplicated malaria*	*0.76 (0.32 – 1.79)*	*65.7% (0.054)*
Gilles et al (1967)[5]	Severe malaria	Healthy	0.85 (0.32 – 2.28)	NA
Modiano et al (2001)[4]	Severe malaria	Healthy	0.66 (0.50 – 0.88)	NA
Mockenhaupt et al (2004)[6]	Severe malaria	Healthy	0.73 (0.47 – 1.12)	NA
May et al (2007)[8]	Severe malaria	Healthy	0.92 (0.75 – 1.13)	NA
Summary[4-6,8]	*Severe malaria*	*Healthy*	*0.83 (0.74 – 0.92)*	*17.2% (0.305)*
Agarwal et al (2000)[3]	Cerebral malaria	Uncomplicated malaria	0.15 (0.004 – 0.93)[b]	NA
May et al (2007)[8]	Cerebral malaria	Healthy	0.64 (0.45 – 0.91)	NA
Guinet et al (1997)[11]	Severe malarial anaemia	Uncomplicated malaria	0 (0 – 7.37)[b]	NA
Agarwal et al (2000)[3]	Severe malarial anaemia	Uncomplicated malaria	0 (0 – 1.49)[b]	NA
Summary[3,11]	*Severe malarial anaemia*	*Uncomplicated malaria*	*0.35 (0.04 – 2.73)*[b]	*0% (0.509)*
May et al (2007)[8]	Severe malarial anaemia	Healthy	0.87 (0.68 – 1.11)	NA
Willcox et al (1983)[10]	Uncomplicated malaria	Healthy	2.8 (0.76 – 11.24)	NA
Modiano et al (2001)[4]	Uncomplicated malaria	Healthy	0.59 (0.45 – 0.77)	NA
Summary[4,10]	*Uncomplicated malaria*	*Healthy*	*1.16 (0.26 – 5.23)*	*84.9% (0.010)*
Haemoglobin AE				
Oo et al (1995)[12]	Severe malaria	Uncomplicated malaria	1.02 (0.59 – 1.80)	NA
Hutagalung et al (1999)[13]	Severe malaria	Uncomplicated malaria	0.11 (0.003 – 0.70)	NA
Summary[12,13]	*Severe malaria*	*Uncomplicated malaria*	*0.41 (0.04 – 3.95)*	*79.5% (0.027)*
Homozygous α-thalassaemia				
Lell et al (1999)[14]	Severe malaria	Uncomplicated malaria	1.1 (0.4 – 2.9)	NA
Allen et al (1997)[15]	Severe malaria	Healthy	0.50 (0.30 – 0.85)	NA

Mockenhaupt et al (2004)[16]	Severe malaria	Healthy	1.27 (0.60 – 2.68)	NA
Williams et al (2005)[17]	Severe malaria	Healthy	0.62 (0.44 – 0.87)	NA
May et al (2007)[8]	Severe malaria	Healthy	0.58 (0.40 – 0.85)	NA
Summary[8,15-17]	*Severe malaria*	*Healthy*	*0.63 (0.48 – 0.83)*	*29.6% (0.234)*
Williams et al (2005)[17]	Fatal malaria	Healthy	0.37 (0.16 – 0.87)	NA
Allen et al (1997)[15]	Severe malarial anaemia	Healthy	0.34 (0.16 – 0.73)	NA
May et al (2007)[8]	Severe malarial anaemia	Healthy	0.53 (0.33 – 0.84)	NA
Summary[8,15]	*Severe malarial anaemia*	*Healthy*	*0.50 (0.35 – 0.72)*	*0% (0.592)*
Heterozygous α-thalassaemia				
Lell et al (1999)[14]	Severe malaria	Uncomplicated malaria	1.3 (0.7 – 2.3)	NA
Allen et al (1997)[15]	Severe malaria	Healthy	0.77 (0.44 – 1.34)	NA
Mockenhaupt et al (2004)[16]	Severe malaria	Healthy	0.67 (0.48 – 0.95)	NA
Williams et al (2005)[17]	Severe malaria	Healthy	0.75 (0.59 – 0.96)	NA
May et al (2007)[8]	Severe malaria	Healthy	0.88 (0.77 – 1.01)	NA
Severe malaria[8,15-17]	*Severe malaria*	*Healthy*	*0.83 (0.74 – 0.92)*	*0% (0.402)*
Williams et al (2005)[17]	Fatal malaria	Healthy	0.60 (0.37 – 1)	NA
May et al (2007)[8]	Cerebral malaria	Healthy	0.80 (0.64 – 1)	NA
Allen et al (1997)[15]	Severe malarial anaemia	Healthy	0.84 (0.41 – 1.7)	NA
May et al (2007)[8]	Severe malarial anaemia	Healthy	0.82 (0.69 – 0.96)	NA
Summary[8,15]	*Severe malarial anaemia*	*Healthy*	*0.86 (0.75 – 0.996)*	*0% (0.651)*
β-thalassaemia				
Willcox et al (1983)[10]	Uncomplicated malaria	Healthy	0.56 (0.36 – 0.86)	NA

Abbreviation: NA: not available. Summary ORs were computed using random-effects models using the DerSimonian & Laird method; the I^2 statistic for heterogeneity was calculated using the Mantel-Haenszel method for the subgroups of meta-analyzed data.

[a] Not included in meta-analyses owing to a lack of reported genotype frequencies in cases and controls.

[b] Study reported combined estimate for HbCC and HbAC.

Table S3. Cross-sectional studies of parasite prevalence and haemoglobinopathies

Source	Location	Subject selection	Ages	Outcome assessed	No. wildtype patients	Haemoglobinopathy	No. patients	Findings
Allison et al (1954)[18]	Uganda	Community survey	5m-5y	Slide-positive *P. falciparum*	247	HbAS	43	*P. falciparum* less prevalent in HbAS
Colbourne et al (1956)[19]	Ghana	Community survey	Children	Slide-positive *P. falciparum*	861	HbAS	139	*P. falciparum* less prevalent in HbAS
Edington et al (1957)[20]	Ghana	Community survey	All ages	Slide-positive *P. falciparum*	726	HbAS	103	Similar prevalence of *P. falciparum* in HbAS and HbAA
						HbAC/HbCC	211	Similar prevalence of *P. falciparum* in HbC and HbAA
Thompson et al (1962)[21]	Ghana	Children of Accra police	1-6y	Slide-positive *P. falciparum*	593	HbAS	123	Similar prevalence of *P. falciparum* in HbAS and HbAA; lower parasite densities in HbAS
						HbAC	101	Similar prevalence of *P. falciparum* in HbAC and HbAA; lower parasite densities in HbAC
Motulsky et al (1966)[22]	Democratic Republic of the Congo	Community survey	17-50y	Slide-positive *P. falciparum*	71	HbAS	6	Similar prevalence and density of *P. falciparum* in HbAS and HbAA
Ringelhann et al (1976)[23]	Ghana	Community survey	<5y	Slide-positive *P. falciparum*	NA	HbAS	NA	Higher prevalence of *P. falciparum* in HbAS
						HbAC	NA	Similar prevalence of *P. falciparum* in HbAC and HbAA
Fleming et al (1979)[24, a]	Nigeria	Community survey	All ages	Slide-positive *P. falciparum*	1925	HbAS	766	Similar prevalence of *P. falciparum* in HbAS and HbAA; lower parasite densities in HbAS
Storey et al (1979)[25, a]	Nigeria	Community survey	All ages	Slide-positive *P. falciparum*	1925	HbAC	21	Similar prevalence and density of *P. falciparum* in HbAC and HbAA
Bernstein et al (1980)[26]	Cameroon	Community survey	<6y	Slide-positive *P. falciparum*	951	HbAS	205	Similar prevalence of *P. falciparum* in HbAS and HbAA
Guggenmoos-Holzmann et al (1981)[27, b]	Nigeria	Febrile outpatients	9m-6y	*P. falciparum* density	503	HbAS	28	Lower densities in HbAS than HbAA
						HbAC	152	Similar densities in HbAC and HbAA
Bienzle et al (1981)[28, b]	Nigeria	Febrile outpatients	9m-6y	Slide-positive *P. falciparum*	503	HbAS	28	Similar prevalence of *P. falciparum* in HbAS and HbAA
						HbAC	152	Similar prevalence of *P. falciparum* in HbAC and HbAA
Willcox et al (1981)[29]	Liberia	Outpatients	>6m	Slide-positive *P. falciparum*	556	HbAS	53	Similar prevalence of *P. falciparum* in HbAS and HbAA
						β-thalassaemia	83	Similar prevalence of *P. falciparum* in thalassaemics and normals
Willcox et al (1983)[30]	Liberia	Community survey	Children	Slide-positive *P. falciparum*	373	β-thalassaemia	159	No difference in prevalence of parasitaemia; less gametocytes and lower parasite densities in β-thalassaemics
Labie et al (1984)[31]	Burkina Faso	Community survey	All ages	Slide-positive *P. falciparum*	261	HbAS	16	Similar prevalence of *P. falciparum* in HbAS and HbAA
						HbAC	76	Similar prevalence of *P. falciparum* in HbAC and HbAA

Allen et al (1992)[32]	The Gambia	Community survey	3-8y	Slide-positive *P. falciparum*	309	HbAS	76	Higher prevalence of *P. falciparum* in HbAS than HbAA
Kar et al (1992)[33]	India	Community survey	All ages	Slide-positive *P. falciparum* or *P. vivax*	604	HbEE	12	Lower prevalence of *P. vivax* and *P. falciparum* in HbEE than HbAA
						HbAE	92	Lower prevalence of *P. vivax* and *P. falciparum* in HbAE than HbAA
Allen et al (1993)[34]	The Gambia	Community survey	3-8y	Slide-positive *P. falciparum*	362	Homozygous α-thalassaemia	7	Similar prevalence of *P. falciparum* in thalassaemics and normals
						Heterozygous α-thalassaemia	102	Similar prevalence of *P. falciparum* in thalassaemics and normals
Aluoch et al (1997)[35]	Kenya	Patients attending a blood testing laboratory	>6m	Slide-positive *P. falciparum*	592	HbAS	116	Similar prevalence of *P. falciparum* in HbAS and HbAA
Ntoumi et al (1997)[36]	Gabon	School children	7-14y	Slide-positive *P. falciparum*	123	HbAS	40	*P. falciparum* less prevalent in HbAS individuals
Mockenhaupt et al (1999)[37]	Nigeria	Community survey	6m-11y	Slide-positive *P. falciparum*	265	Homozygous α-thalassaemia	43	Similar prevalence of *P. falciparum* in thalassaemics and normals
						Heterozygous α-thalassaemia	186	Similar prevalence of *P. falciparum* in thalassaemics and normals
Wambua et al (2006)[38]	Kenya	Community survey	<5y	Slide-positive *P. falciparum*	320	Homozygous α-thalassaemia	171	Similar prevalence of *P. falciparum* in thalassaemics and normals
						Heterozygous α-thalassaemia	543	Similar prevalence of *P. falciparum* in thalassaemics and normals
Veenemans et al (2008)[39]	Kenya and Tanzania	Community survey	6m-8y	Slide-positive *P. falciparum*	317	Homozygous α-thalassaemia	92	Similar prevalence of *P. falciparum* in thalassaemics and normals
						Heterozygous α-thalassaemia	345	Similar prevalence of *P. falciparum* in thalassaemics and normals
Fowkes et al (2008)[40]	Papua New Guinea	Community survey	1-17y	Slide-positive *P. falciparum*	39	Homozygous α-thalassaemia	311	Similar prevalence of *P. falciparum* in thalassaemics and normals
						Heterozygous α-thalassaemia	205	Similar prevalence of *P. falciparum* in thalassaemics and normals
Shekalaghe et al (2009)[41]	Tanzania	Community survey	All ages	Slide- or PCR-positive *P. falciparum*	295	Homozygous α-thalassaemia	14	Similar prevalence of *P. falciparum* in thalassaemics and normals
						Heterozygous α-thalassaemia	100	Similar microscopy prevalence, higher PCR-prevalence in thalassaemics than normals
Danquah et al (2010)[42]	Ghana	Community survey	6m-9y	Slide- or PCR-positive *P. falciparum*	1496	HbAS	157	Similar prevalence of *P. falciparum* in HbAS and HbAA, but lower densities in HbAS
						HbCC	16	Similar prevalence and density of *P. falciparum* in HbCC and HbAA
						HbAC	415	Similar prevalence and density of *P. falciparum* in HbAC and HbAA
Jeremiah et al (2010)[43]	Nigeria	Community survey	1-8y	Slide-positive *P. falciparum*	210	HbAS	30	Similar prevalence of *P. falciparum* in HbAS and HbAA

Abbreviations: NA, not available; Hb, hemoglobin

[a] Studies reported different outcomes for the same cohort.

[b] Studies reported different outcomes for the same cohort.

Table S4. Cross-sectional studies of parasite prevalence in pregnancy and haemoglobinopathies

Source	Location	Timing	n	Variants	% primigravidae	Findings
Hamilton et al (1972)[44]	Uganda	Antenatal	1327	HbAS	31.2	Higher prevalence of antenatal *P. falciparum* parasitaemia in HbAS (13.5%) v. HbAA (9.1%) women
Fleming et al (1984)[45]	Nigeria	Antenatal	228	HbAS, HbAC	100	HbAS associated with non-significantly lower antenatal prevalence of *P. falciparum* compared with HbAA (17% v. 27%); no association with HbAC
Mockenhaupt et al (2000)[46]	Ghana	Antenatal	530	HbAS, HbAC, α-thalassaemia	24.5	No association between HbAS, HbAC, homozygous or heterozygous α-thalassaemia and antenatal *P. falciparum* parasitaemia
Bouyou-Akotet et al (2003)[47]	Gabon	Antenatal	311	HbAS	69.8	No association between HbAS and antenatal *P. falciparum* parasitaemia
O'Donnell et al (2006)[48]	Papua New Guinea	Delivery	913	α-thalassaemia	36.3	No association between homozygous or heterozygous α-thalassaemia and placental malaria, peripheral parasitaemia at delivery, preterm delivery, or birth weight

Abbreviation: Hb, hemoglobin.

Supplementary references

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