PRISMA 2020 Checklist

Section/topic	Item #	Checklist item	Location in manuscript
TITLE	1	Identify the report as a systematic review.	Title: "Epistatic interactions among coinherited malaria-protective red-blood-cell polymorphisms in endemic regions: a systematic review."
ABSTRACT	2	See the PRISMA 2020 for Abstracts checklist.	Structured abstract on pp. 2–3 (with Background, Objective, Methods, Results, Conclusions)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction (paras 1–2; lines 1–18): "Malaria remains one of the most powerful selective pressures…"
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction (final para; lines 55–63): "To characterise how epistatic interactions among coinherited … modify malaria risk across the infection-to-mortality spectrum."
METHODS			

Eligibility criteria	5	Specify inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods “Eligibility criteria” (lines 74–102) and Table S1 in Supplement.
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched; date of last search.	Methods “Information sources and search strategy” (lines 105–125); last search 1 July 2023; Supplement S2 contains full list.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including filters and limits used.	Methods (lines 110–116) refer to Supplement S2, which provides exact search strings for PubMed, Embase, Web of Science, and Cochrane Library.
Selection process	8	Specify methods used to decide whether	Methods “Study selection” (lines 126–148): Two reviewers independently screened

		a study met the inclusion criteria, including number of reviewers and whether they worked independently.	titles/abstracts (κ = 0.82), then full texts; disagreements resolved by consensus.
Data collection process	9	Specify methods used to collect data, number of reviewers, whether they worked independently, and any automation tools used.	Methods “Data extraction and management” (lines 149–178): Two reviewers independently extracted into REDCap; discrepancies adjudicated by a senior reviewer.
Data items – outcomes (10a)	10a	List and define all outcomes for which data were sought, and how results were selected.	Methods “Data extraction” (lines 150–162): Outcomes include infection prevalence, parasite density, uncomplicated malaria, severe malaria, and mortality.
Data items – other variables (10b)	10b	List and define all other variables	Methods (lines 160–178): Extracted study design, setting, sample size, age/sex,

		(participant, intervention characteristics, funding). Describe assumptions for missing/unclear information.	genotyping methods, covariates, funding, conflicts, and interaction definitions.
Study risk-of-bias assessment	11	Specify methods to assess risk of bias, including tools used, reviewers, independence, and any automation tools.	Methods “Risk-of-bias assessment” (lines 179–196): Adapted NOS with 7 domains; two reviewers independently rated; third resolved disagreements; Supplement S2 Table S2.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference).	Methods “Synthesis” (lines 207–214): Primary measures were odds ratios (ORs), incidence-rate ratios (IRRs), and geometric mean ratios (GMRs) with 95 % CIs.
Synthesis methods (13a) – eligibility for synthesis	13a	Describe process used to decide which studies were	Methods (lines 215–225): Grouped studies by genotype pair; only pairs with ≥ 3 studies

		eligible for each synthesis.	underwent vote-counting; others narratively described.
Synthesis methods (13b) – data preparation	13b	Describe methods required to prepare data for presentation or synthesis, such as handling missing summary statistics.	Methods (lines 226–232): Converted HRs to IRRs where needed; imputed CIs when not reported; standardized allele nomenclature across studies.
Synthesis methods (13c) – display results	13c	Describe methods to tabulate or visually display results of individual studies and syntheses.	Methods (lines 233–245): Used vote-count tables (Table 2), heat maps (Figure 3), and forest plots (Figures 4–5) generated with ggplot2.
Synthesis methods (13d) – synthesis rationale	13d	Describe methods used to synthesize results and rationale. If meta-analysis, describe models, heterogeneity	Methods (lines 246–254): No meta-analysis due to heterogeneity; synthesised by directionality and mechanistic plausibility; R 4.2.0 and SWiM guidance used.

		measures, software.	
Synthesis methods (13e) – heterogeneity exploration	13e	Methods used to explore possible causes of heterogeneity (e.g., subgroup analysis, meta-regression).	Methods (lines 255–264): Explored heterogeneity by age, sex, transmission setting, and assay method; reported in "Context dependence" section (lines 552–576).
Synthesis methods (13f) – sensitivity analyses	13f	Describe any sensitivity analyses conducted.	Methods (lines 265–274): Sensitivity analyses excluding studies with Serious RoB; results unchanged (Supplement S3 Fig S1).
Reporting bias assessment	14	Describe methods used to assess risk of bias due to missing results (reporting biases).	Methods (lines 275–281): No formal assessment (e.g., funnel plots) due to < 10 studies per comparison; noted as limitation.
Certainty assessment	15	Describe methods used to assess certainty in the body of evidence (e.g., GRADE).	Methods "Certainty of evidence (GRADE)" (lines 279–314): GRADE domains described; two reviewers; GRADEpro software v.3.2 used; Supplement S4 for GRADE evidence profiles.

RESULTS			
Study selection (16a)	16a	Describe the results of the search and selection process, ideally using a flow diagram.	Results “Study selection” (lines 335–366); PRISMA flow diagram (Figure 1).
Study selection (16b)	16b	Cite studies that might appear to meet inclusion criteria but were excluded, and explain why.	Results (lines 361–366): Table S5 lists 27 full-text exclusions with reasons (e.g., no genotype co-inheritance).
Study characteristics	17	Cite each included study and present its characteristics.	Results “Characteristics of included studies” (lines 395–416); Table 1 provides country, design, sample sizes, genotypes, and outcomes.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results “Risk of bias assessment” (lines 367–381); Table S6 and Figures 6–7 display domain-level and overall RoB.
Results of individual studies	19	For all outcomes, present for each study: summary	Results sections (lines 467–526), narrative summaries, and Figures 4–5; Table 2 lists vote

		statistics for each group and an effect estimate with precision.	counts and representative effect sizes per genotype pair.
Results of syntheses (20a)	20a	For each synthesis, briefly summarise the characteristics and RoB of contributing studies.	Results “Directions of epistatic interaction” (lines 517–535) and Table 2 vote counts; RoB mentioned in text.
Results of syntheses (20b)	20b	Present results of all statistical syntheses; if meta-analysis, present summary estimate, precision and heterogeneity.	Not applicable (no meta-analysis).
Results of syntheses (20c)	20c	Present results of investigations of possible causes of heterogeneity.	Results “Context dependence” (lines 552–576) describes age, sex and setting modifiers; no formal meta-regression.

Results of syntheses (20d)	20d	Present results of sensitivity analyses.	Results (lines 578–586) summarise sensitivity analyses excluding high-RoB studies (Supplement S3 Fig S1).
Reporting biases (21)	21	Present assessments of risk of bias due to missing results for each synthesis assessed.	Not formally done; noted in Methods (lines 275–281) and Limitations (lines 614–620).
Certainty of evidence (22)	22	Present assessments of certainty in the body of evidence for each outcome.	Results "Certainty of evidence (GRADE)" (lines 314–334) and Summary-of-Findings Table 3 display GRADE ratings per interaction-outcome.
DISCUSSION			
Discussion — interpretation	23a	Provide a general interpretation of the results in context of other evidence.	Discussion (lines 530–557), first two paragraphs.
Discussion — limitations of evidence	23b	Discuss limitations of the evidence included.	Discussion "Study strengths and limitations" (lines 614–629).

Discussion — limitations of review processes	23c	Discuss limitations of the review methods.	Discussion (lines 631–640): "Our search may have missed grey literature… risk-of-bias tool not validated in genetic studies…"
Discussion — implications	23d	Discuss implications for practice, policy, and future research.	Discussion "Implications for clinical risk prediction…" (lines 630–650); final paragraph.
OTHER INFORMATION			
Registration and protocol (24a)	24a	Provide registration information for the review, including register name and registration number.	Methods "Protocol and registration" (lines 68–73): PROSPERO CRD42023345678.
Registration and protocol (24b)	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods (lines 68–73): Protocol publicly archived at https://osf.io/xyz.

Registration and protocol (24c)	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods (lines 74–76): “Amendments to eligibility criteria (added adult cohorts) documented in Supplement S1.”
Support (25)	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors.	Declaration “Funding” (lines 688–697): No dedicated funding; institutional support from Wellcome Trust; sponsors had no role.
Competing interests (26)	26	Declare any competing interests of review authors.	Declaration “Competing interests” (lines 704–706): All authors declare no competing interests.
Availability of data, code, and other materials (27)	27	Report which template forms, extracted data, analysis code, and other materials are publicly	Declaration “Data and materials” (lines 707–713): Data extraction sheet and R code available at https://github.com/username/epistasis_review; Zenodo DOI provided.

		available and where.	

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