Original Article

Glucose-6-phosphate dehydrogenase deficiency and risk of malaria: systematic review and meta-analysis

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Background: Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme expressed ubiquitously and catalyzes the initial step of the pentose phosphate pathway. G6PD deficiency adversely affects red blood cells (RBCs), leading to the most common inherited hematological disorder. The present study aims to assess the prevalence of G6PD deficiency among malaria-infected and healthy individuals.

Methods: Publications related to G6PD deficiency and malaria were searched through the databases. The prevalence of G6PD deficiency phenotype was assessed using the meta-analysis for Jamovi R (MAJOR) module from the Jamovi library. To estimate the pooled risk ratio (RR) of G6PD deficiency among patients with malaria, we utilized the Review Manager 5.4.1 software.

Results: A total of 33 datasets sourced from 27 studies were included in the present meta-analysis. The estimated average prevalence was found to be 11%. Analysis of RR indicated that the G6PD deficiency does not significantly differ between malaria patients and healthy individuals [RR =0.91, 95% confidence interval (CI): 0.76–1.10; P=0.35]. The study identified a high level of heterogeneity between studies (I^2=72%). Stratified analysis reveals that the G6PD deficient allele is associated with protection against malaria, specifically when the infection is exclusively caused by *P. falciparum* (RR =0.77, 95% CI: 0.61–0.97; P=0.03) in populations where the prevalence of the G6PD deficient allele exceeds 13% (RR =0.72, 95% CI: 0.57–0.91; P=0.006).

Conclusions: As the independent studies included in this meta-analysis employ varied techniques for detecting malaria and G6PD deficiency, these results should be interpreted with caution, and further investigations are warranted.

Keywords: Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency); malaria; prevalence; meta-analysis

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme expressed ubiquitously, possessing housekeeping properties. It plays a crucial role in maintaining the integrity and proper function of red blood cells (RBCs), and it is indispensable in glucose metabolism. G6PD catalyzes the initial step of the pentose phosphate pathway, converting glucose-6-phosphate to 6-phosphogluconolactone and generating nicotinamide adenine dinucleotide phosphate (NADPH) (1). NADPH serves as an electron donor, providing the reducing energy necessary for the regeneration of reduced glutathione. Consequently, NADPH sustains glutathione proteins and enzymes in their reduced state, safeguarding RBCs against oxidative damage (2). This mechanism represents the primary source of NADPH in erythrocytes (3). Therefore, G6PD deficiency adversely affects RBCs, leading to the most common inherited haematological disorder.

The gene encoding the G6PD enzyme is located on Xq28 and is inherited as an X-linked blood disorder. Numerous missense mutations in the G6PD gene have been documented to decrease the stability and activity of the enzyme. RBCs with reduced G6PD enzyme levels are susceptible to cell lysis following exposure to oxidative stress conditions (4). Due to this, RBCs infected by the malaria parasite are also destroyed by phagocytosis, thereby suppressing parasite growth within the RBC (5,6). Further, G6PD deficiency disrupts the oxidative stress in RBCs created by the infestation of malarial parasite, which makes the RBCs less hospitable to the parasite (7). Consequently, a direct correlation between *P. falciparum* malaria prevalence and the incidence of G6PD deficiency has been reported (8). Globally, approximately 400 million individuals are affected by G6PD deficiency disorder, with prevalence ranging from 8% to 30% in malaria-endemic regions (9). Furthermore, anti-malarial drugs such as the 8-aminoquinoline class (primaquine, tafenoquine), chloroquine (4-aminoquinoline), quinolones, chloramphenicol, sulfonamides, nitrofurantoin (antibiotics), dapsone, and phenazopyridine induce oxidative stress, which may not be adequately neutralized by G6PD-deficient RBCs, leading to hemolytic crises (10). However, primaquine and tafenoquine are the only anti-malarial drugs available to prevent the spread of *P. vivax* malaria, despite causing dangerous side effects in G6PD-deficient individuals (11). Consequently, mild or low dosages of primaquine or tafenoquine are prescribed for G6PD-deficient patients. Heterozygous G6PD-deficient females are more protected from malaria compared to G6PD-deficient hemizygous males or homozygous females, although this protection remains questionable (5). However, it's important to note that the relationship between G6PD deficiency and malaria is influenced by various factors, including the specific genetic variants of G6PD, the prevalence of malaria transmission in a given population, and other genetic and environmental factors specific to the host. Therefore, the present study aims to assess the prevalence of G6PD deficiency among malaria-infected and healthy individuals using meta-analysis. We present this article in accordance with the PRISMA reporting checklist (available at https://jlpm.amegroups.org/article/view/10.21037/jlpm-25-13/rc) (6).

Highlight box

Key findings

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency shows no overall significant association with malaria, but offers protection against *P. falciparum* in high-prevalence regions.

What is known and what is new?

- G6PD deficiency is the most common inherited blood disorder and affects red blood cell (RBC) stability.
- Its potential protective role against malaria, especially Plasmodium falciparum, has been suggested in past studies.
- Prevalence and effects of G6PD deficiency vary geographically and ethnically.
- This study found no significant overall association between G6PD deficiency and malaria infection.
- Stratified analysis reveals a protective effect against *P. falciparum* in populations where G6PD deficiency is more common (>13% prevalence).
- It highlights the importance of population-level genetic context and malaria species when evaluating G6PD's role.

What is the implication, and what should change now?

- G6PD deficiency may offer protection against *P. falciparum* in high-prevalence regions.
- Future research and malaria control strategies should consider G6PD prevalence and malaria species in specific populations.

Methods

Study search and selection

Publications related to G6PD deficiency and malaria were systematically searched through the PubMed and Google Scholar databases. The search utilized keywords including G6PD, malaria, and prevalence of G6PD deficiency, covering papers published up to January 2024. Inclusion criteria were established for the selection of articles as

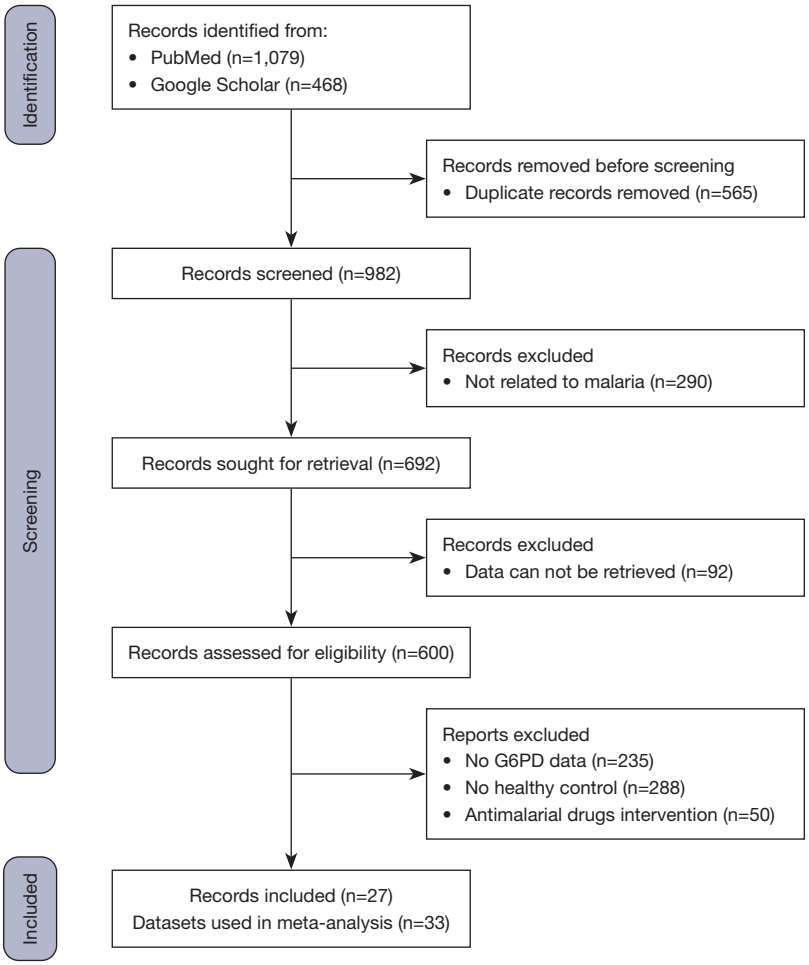

Figure 1 PRISMA diagram showing the process of study retrieval for meta-analysis. G6PD, glucose-6-phosphate dehydrogenase.

follows: (I) original studies delineating the relationship between G6PD deficiency and malaria; (II) studies reporting G6PD prevalence; (III) inclusion of data on G6PD deficiency and the number of patients with malaria, as well as data on healthy individuals. Publications unrelated to G6PD deficiency and malaria were excluded. Two authors independently screened titles and abstracts of the retrieved papers and identified 27 relevant papers for further assessment. Data extraction encompassed the following information from all eligible studies: authors' names, year of study, country, study design, prevalence of G6PD deficiency in malaria patients and healthy subjects (Table S1). The flow of the study selection process is illustrated in *Figure 1*.

Statistical analysis

The pooled prevalence of G6PD deficiency phenotype in both malaria patients and healthy subjects was assessed using the meta-analysis for Jamovi R (MAJOR) module from the Jamovi library. Heterogeneity between studies was measured using the I2 statistic. The Review Manager 5.4.1 software was employed to estimate the pooled risk ratio (RR) of having G6PD deficiency in patients with malaria. The random-effects model was utilized to pool the data. Publication bias was evaluated through visual inspection of the funnel plot.

Results

The present meta-analysis included 33 prevalence estimates to assess the prevalence of G6PD deficiency in both malaria and healthy individuals. The observed prevalence of G6PD deficiency ranged from 1% to 30%, mainly due to between-study variance (I^2=72%). The estimated average prevalence

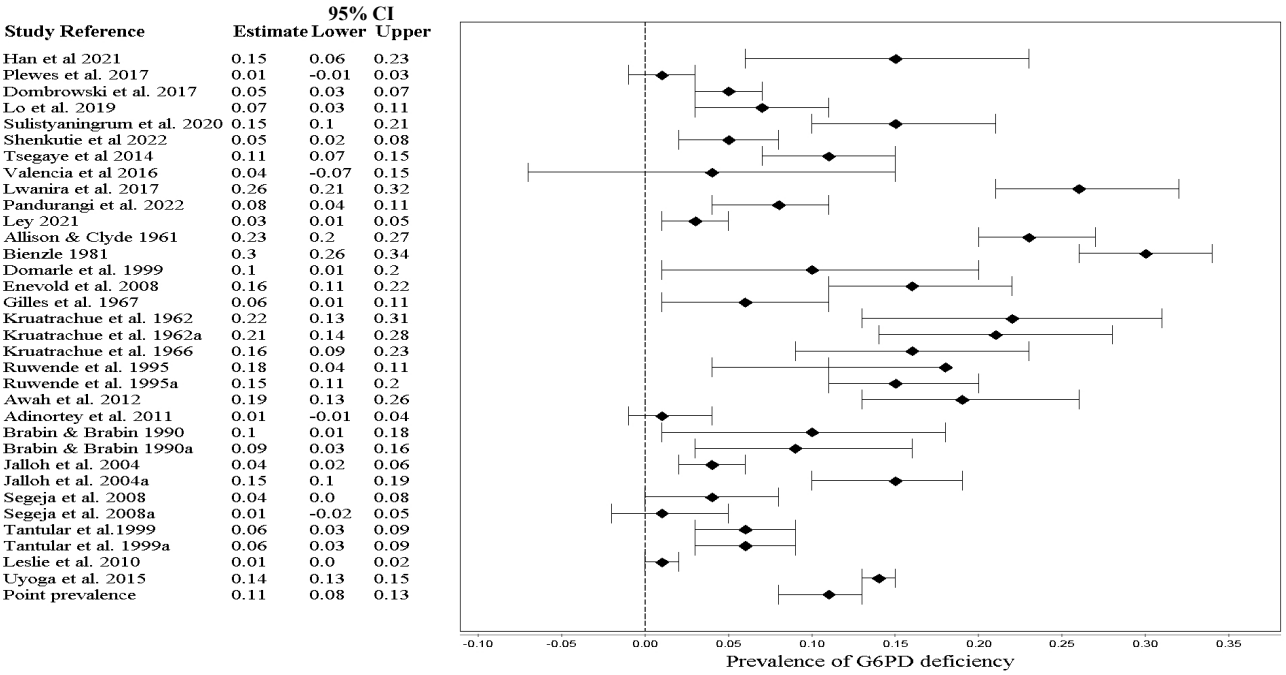

Figure 2 Forest plot showing average prevalence of G6PD deficiency in malaria patients. CI, confidence interval; G6PD, glucose-6-phosphate dehydrogenase.

was 11% [95% confidence interval (CI): 8–13%] (*Figure 2*). The individual RRs, along with the pooled RR, were illustrated in the forest plot (*Figure 3*). A RR of 0.91 with a 95% CI of 0.76–1.10 indicates that G6PD deficiency does not significantly differ between malaria patients and healthy individuals. Substantially high between-study heterogeneity observed in this study suggests potential variations among studies (I^2=72%). Subgroup analysis based on the ethnicity, frequency of the G6PD allele and type of malaria parasite was conducted (*Table 1*, Figure S1). Subgroup analysis by ethnicity revealed that the RR of G6PD deficiency in patients with malaria compared to healthy individuals varied among Asian (RR =0.95, 95% CI: 0.66–1.38, P=0.80), African (RR =0.86, 95% CI: 0.68–1.07, P=0.18), and Caucasian (RR =1.50, 95% CI: 0.44–5.16, P=0.52) populations. This suggests that G6PD deficiency is not significantly associated with malaria in Asian, African, and Caucasian populations.

Stratification by G6PD deficiency allele prevalence revealed that protection against malaria was observed among studies with G6PD deficiency allele prevalence >13 (RR =0.72, 95% CI: 0.57–0.91, P=0.006), but not in studies with G6PD deficiency allele prevalence ≤13 (RR =1.33, 95% CI: 0.84–1.50, P=0.42) (*Table 1*, Figure S2). Additional stratification by single malaria parasite (*P. falciparum*) and mixed infections (*P. falciparum* with other species) revealed that protection against malaria was observed among studies where malaria was caused by *P. falciparum* only (RR =0.77, 95% CI: 0.61–0.97, P=0.03) (*Table 1*, Figure S3). However, the protective effect of the G6PD deficiency allele against malaria was not observed among studies where malaria was caused by mixed infections (RR =1.20, 95% CI: 0.87–1.64, P=0.26). The shape of the funnel plots did not reveal obvious asymmetry, indicating no evidence of major publication bias (Figure S4).

Discussion

In 1956, a group of researchers for the first time reported the deficiency of the G6PD enzyme in primaquine-sensitive erythrocytes (12). Subsequently, an increased frequency of G6PD deficiency was reported in malaria-endemic regions due to resistance to malaria (13). Furthermore, a 2–80 times greater infestation by malaria parasites was observed in G6PD nondeficient cells compared to deficient cells (14), indicating that G6PD-deficient cells provided protection against malaria. Although individuals with G6PD deficiency are mostly asymptomatic, acute hemolytic anemia may

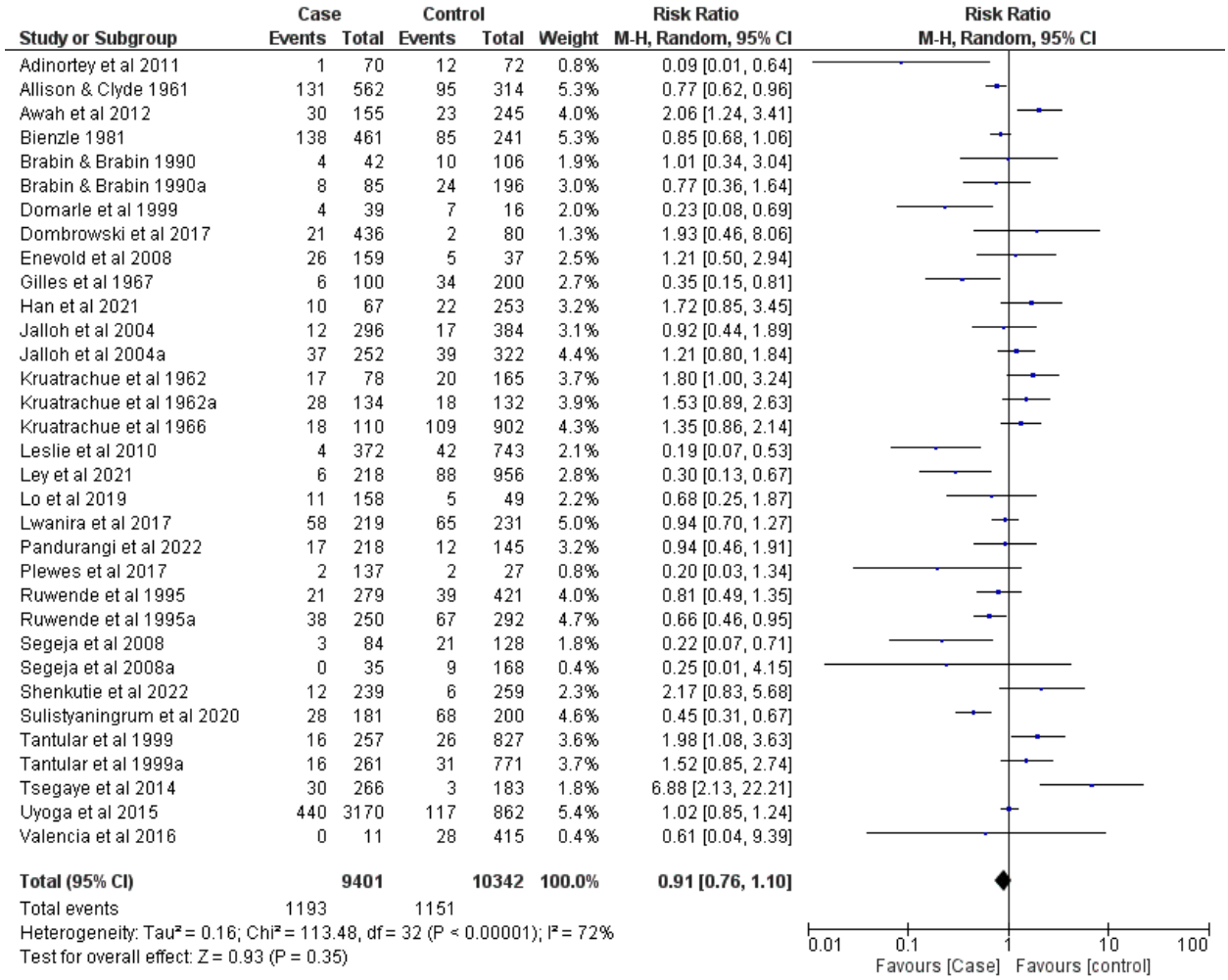

Figure 3 Forest plot showing risk ratios of having G6PD deficiency in patients with & without malaria. CI, confidence interval; G6PD, glucose-6-phosphate dehydrogenase; M-H, Mantel-Haenszel.

Table 1 Subgroup analysis based on the ethnicity, frequency of the G6PD allele and type of malaria parasite

Subgroup	No. of papers	Heterogeneity		Association	
		I^2, %	P value	Risk ratio (95% CI)	P value
Ethnicity					
Asia	13	79	<0.001	0.95 (0.66–1.38)	0.80
Africa	18	69	<0.001	0.86 (0.68–1.07)	0.18
Caucasian	2	0	0.46	1.50 (0.44–5.16)	0.52
Frequency of the G6PD deficient allele					
Frequency >13	12	73	<0.001	0.72 (0.57–0.91)	0.01
Frequency ≤13	21	65	<0.001	1.13 (0.84–1.50)	0.42
Malaria parasite					
P. falciparum (alone)	14	69	<0.001	0.77 (0.61–0.97)	0.03
P. falciparum and other strains	16	72	<0.001	1.20 (0.87–1.64)	0.26

CI, confidence interval; G6PD, glucose-6-phosphate dehydrogenase.

emerge when erythrocytes are exposed to drugs or infections, causing oxidative stress. However, the severity of hemolysis is primarily determined by the level of oxidative stress and the degree of enzymatic malfunction.

A plethora of previous studies have indicated that G6PD deficiency offers protection against malaria due to its hemolytic property (5,15-17). Therefore, G6PD deficiency is relatively frequent in malaria-endemic areas (18). In malaria-endemic areas of Eastern Indonesia, G6PD deficient subjects showed a lower risk of malaria than normal individuals (19). In females, G6PD deficiency is associated with *P. falciparum* infection, while in males, it is associated with *P. vivax* infection (19). In contrast to this, the malaria-endemic region in the Western Brazilian Amazon reported similar malaria episodes in both G6PD deficient and normal individuals, indicating that G6PD deficiency probably does not protect against *P. vivax* infection (20). Furthermore, *P. vivax* infestation was not significantly different between G6PD-deficient and G6PD-normal malaria patients in Ethiopia (21). In eastern Ethiopia, the prevalence of G6PD deficiency is low but correlated with a history of previous malaria infection (22). Although G6PD deficiency is uncommon among Bengalis of Bangladesh, patients with G6PD deficiency exhibited relatively substantially extended symptoms prior to admission compared to G6PD normal cases (23). Significantly lower malaria parasite infestation and less severe clinical symptoms were found in individuals with G6PD deficiency and sickle cell trait, compared to normal subjects (24). However, some studies reported that clinical complications such as anemia, jaundice, and blood transfusions were more frequent in G6PD deficient individuals than in normal individuals (20,25,26).

Some previous papers had reported that there is no association between G6PD deficiency and occurrence of uncomplicated *P. falciparum* malaria except for heterozygous girls (27). A previous meta-analysis demonstrated that G6PD deficiency can potentially protect against uncomplicated malaria in African countries (28). This study also showed that there was no link between G6PD deficiency and severe malaria or other malaria species (28). Another contemporary meta-analysis also supported the notion that G6PD deficiency offers protection against severe malaria (29).

The findings of the current meta-analysis indicate that G6PD deficiency is not associated with protection against malaria in the overall population, including Asian, African, and Caucasian groups. However, stratified analysis reveals that the G6PD deficient allele is associated with protection against malaria, specifically when the infection is exclusively caused by *P. falciparum* in populations where the prevalence of the G6PD deficient allele exceeds 13%. These results should be interpreted with caution due to variations in the detection techniques for malaria and G6PD deficiency among the independent studies included in this meta-analysis. Not all of the selected articles, as indicated in Table S1, employed genotyping to identify G6PD deficiency, which may contribute to the high variability observed between studies. For example, a study that assessed the phenotype using the CareStart® method reported a sensitivity of only 0.68. Other studies relied on the older fluorescence spot test method, which also exhibits low sensitivity. A sub-analysis stratifying by sex was not performed, which may constitute an important limitation for a condition that is transmitted through sex-linked inheritance. Other potential limitations are the inconsistent definition of G6PD deficiency between studies, as well as the allelic heterogeneity of the G6PD locus. Therefore, further investigations are warranted to furnish researchers with conclusive evidence regarding whether the G6PD deficient allele serves as a genetic predictor of milder malaria in different populations.

Conclusions

This meta-analysis indicates that the G6PD deficient allele is associated with protection against malaria, specifically when the infection is exclusively caused by *P. falciparum* in populations with G6PD deficient allele frequency is >13%. Given the methodological variations and high heterogeneity between studies included in this meta-analysis, further well-designed studies with a large sample size and reliable diagnostic and genotyping methods are needed to validate this study's findings.

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None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-25-13/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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