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REVIEW

Impact of Malaria in Pregnancy on Risk of Malaria in Young Children: Systematic Review and Meta-Analyses

Sangshin Park,[1,2,3] Christina E. Nixon,[1,4] Olivia Miller,[5] Nam-Kyong Choi,[6] Jonathan D. Kurtis,[1,4] Jennifer F. Friedman,[1,2,a] and Ian C. Michelow[1,2,a]

[1]Center for International Health Research, Rhode Island Hospital, Providence, Rhode Island, USA, [2]Department of Pediatrics, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA, [3]Graduate School of Urban Public Health, University of Seoul, Seoul, Republic of Korea, [4]Department of Pathology and Laboratory Medicine, The Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA, [5]Department of Global Health, DePauw University, Greencastle, Indiana, USA, [6]Department of Health Convergence, Ewha Womans University, Seoul, Republic of Korea

Background. Our objective was to quantify the risk of acquiring malaria among progeny of women with malaria during pregnancy.

Methods. We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library for eligible prospective studies. The primary predictor was malaria during pregnancy defined as placental malaria, parasitemia, clinical malaria, or pregnancy-associated malaria. Primary outcomes were parasitemia or clinically defined malaria of young children. We performed meta-analyses to pool adjusted risk estimates using a random-effects model.

Results. Nineteen of 2053 eligible studies met inclusion criteria for the systemic review. Eleven of these studies were quantitative and were included in the meta-analyses. The pooled adjusted odds ratio (aOR) or adjusted hazard ratio (aHR) of malaria during pregnancy for detection of parasitemia in young children were 1.94 (95% confidence interval [CI], 0.93–4.07; $P = .08$) and 1.46 (95% CI, 1.07–2.00; $P < .001$), respectively. The pooled aOR or aHR for clinically defined malaria in young children were 2.82 (95% CI, 1.82–4.38; $P < .001$) and 1.31 (95% CI, 0.96–1.79; $P = .09$), respectively.

Conclusions. Our results confirmed that malaria during pregnancy significantly increased the overall risk of malaria in young children via indeterminate mechanisms and emphasize the urgent need to implement safe and highly effective strategies to prevent malaria during pregnancy.

Keywords. malaria; parasitemia; pregnancy; placenta; infant.

Malaria is a parasitic, vector-borne tropical and subtropical disease that affects individuals residing in 87 countries [1]. *Plasmodium falciparum* is the most common cause of human malaria with potentially severe complications that disproportionately affect pregnant women and young children [2, 3]. In 2017, malaria led to an estimated 219 million cases and 435 000 deaths worldwide, with children under 5 years accounting for 61% of all deaths [1]. Approximately 125 million women living in malaria-endemic areas become pregnant each year [4]. Primigravid women are most susceptible to malaria because they do not possess natural immunity to the Var2CSA variant of *Pf*EMP1 exposed on the surface of erythrocytes infected with *P falciparum* strains that selectively sequester in the placenta and adhere to chondroitin sulfate A [5]. It is postulated that in the absence of pregnancy-specific interventions, approximately 45% of pregnant women in Africa would be exposed to malaria, almost half of whom would develop placental malaria (PM) [6].

Malaria during pregnancy is associated with abortion, congenital malaria, infant anemia, intrauterine growth restriction, low birth weight, preterm delivery, and stillbirth [7]. Systematic reviews and meta-analyses have demonstrated that malaria prevention during pregnancy is associated with decreased risk of low birth weight and neonatal mortality [8, 9]. The precise mechanisms by which pregnancy-associated malaria affects fetuses and infants are unknown. In addition to direct invasion and infection of fetuses that occurs rarely, there is growing evidence to suggest that malaria infection during pregnancy can modulate fetal immune responses and influence the subsequent risk for young children of acquiring malaria. In multigravid women particularly, malaria may induce fetal immune priming that leads to increased susceptibility of infants to malaria [10]. However, several cohort studies that have studied the impact of pregnancy-associated malaria on young children have demonstrated varying outcomes hypothesized to be related to timing of maternal infection, gravidity, presence of PM, or common exposure of mother-infant dyads to infectious mosquitoes [11–14].

Knowledge about the effects of malaria during pregnancy on young children's risk for acquiring malaria is urgently needed to inform evidence-based interventions and to mitigate the

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[a]I. C. M. and J. F. F. contributed equally to this manuscript.

Correspondence: Sangshin Park, DVM, MPH, PhD, Graduate School of Urban Public Health, University of Seoul, 163 Seoulsiripdae-ro, Dongdaemun-gu, Seoul 02504, Republic of Korea (spark@uos.ac.kr).

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attributable morbidity and mortality in early childhood [15, 16]. In this systematic review and meta-analysis, we investigated the direct relationship between malaria during pregnancy and the risk posed to offspring of acquiring malaria in early childhood, and we also evaluated the quality of the evidence.

METHODS

We performed a systematic review and meta-analyses according to standardized guidelines of PRISMA and MOOSE [17, 18].

Literature Search and Study Selection

We searched the relevant medical literature using MEDLINE, EMBASE, CINAHL, and the Cochrane Library from inception through August 28, 2017 without restrictions for language or study design. We developed the search strategy based on synonymous and analogous associations with predictors and outcomes. The following thesaurus search terms (eg, Medical Subject Heading terms) were used: malaria AND pregnancy AND (child OR infant). Each thesaurus term was "exploded" to retrieve related subheadings. To find additional relevant publications, we considered all citations of relevant studies including literature reviews.

Cohort and case-control studies were eligible for inclusion provided they met the following criteria: (1) infection with *P falciparum* was confirmed in mothers during pregnancy or at delivery—types of maternal infection included PM, parasitemia, clinical malaria, or the all-inclusive term, pregnancy-associated malaria (PAM); (2) young children were evaluated for evidence of *P falciparum* parasitemia and clinical manifestations of malaria for at least the first 3 months of life; (3) infection with *P falciparum* in pregnant women and children was confirmed with a positive blood smear, commercial rapid diagnostic test (RDT), or polymerase chain reaction (PCR) assay; and (4) the direct relationship between malaria during pregnancy and the child's malaria infection was assessed using linked mother-infant data. All eligible studies that met the inclusion criteria were included in the systematic review. Only studies that reported adjusted odds ratios (aORs) or adjusted hazard ratios (aHRs) were included in the meta-analyses to measure adjusted pooled effect sizes.

We excluded review articles, animal studies, and data derived from cross-sectional epidemiological analyses. Furthermore, we did not analyze data from asymptomatic pregnant women or infants from a single article [19] because the sparse data precluded meaningful analysis. Two papers that reported relative risk (RR) or relative rate ratio to measure effect sizes were ineligible because it was not possible to integrate these measures with OR based on the high prevalence of malaria in study areas [20, 21]. We did not include one study that reported HR derived from repeated measures of sequential episodes of parasitemia or clinical malaria because it could not accurately be pooled with HRs from the other eligible studies [14]. One study provided data about maternal malaria infections for each trimester of pregnancy; we used data only for the third trimester [13].

S.P. and I.C.M. independently searched the literature and selected eligible articles. Statistical agreement between the reviewers was measured with the Cohen's kappa coefficient.

Data Extraction

S.P. and O.M. independently extracted data from each article. Differences between reviewers were resolved through arbitration by J.F.F. Information about authors, study site, sample size, follow-up period, exposure, outcome, measure of effect, unadjusted and adjusted effect sizes, and factors that required adjustment were systematically collated. The primary predictor of interest was malaria infection during pregnancy as determined by parasitological or clinical measures. We accepted the definitions of the types of maternal infection as described in the articles: PM required the presence of malaria parasites or pigment in a placental blood smear or biopsy; parasitemia required the presence of *P falciparum* in peripheral blood; clinical malaria was defined by the presence of fever with symptoms described in the relevant articles with evidence of malaria parasites in their peripheral blood; PAM included clinical signs as well as evidence of malaria parasites in peripheral blood or the placenta. For outcomes of interest in young children, parasitemia was defined as the presence of malaria parasites in peripheral blood and clinical malaria was defined as fever and other symptoms associated with parasitemia. Malaria parasitemia was detected by blood smear microscopy, commercial RDTs, or PCR assays.

Quality Assessment

S.P. and C.E.N. independently assessed the quality of evidence describing the relationship between malaria infection during pregnancy and the risk of malaria in the offspring using the modified Newcastle-Ottawa Quality Scale (NOS) in order to eliminate bias [22]. This scale assesses the following star-awarded criteria: (1) Selection - representativeness of the exposed cohort (truly or somewhat [eg, collections of participants from at least 3 or more communities] = 1 star), selection of the nonexposed cohort (drawn from the same community as the exposed cohort = 1 star), ascertainment of exposure (laboratory-based determination = 1 star), and demonstration that the outcome of interest was not present at the start of the study (confirmation of the absence of congenital malaria = 1 star); (2) Comparability - comparability of cohorts on the basis of the design or analysis (adjustment for bed net use = 1 star; adjustment for birth season = 1 star); (3) Outcome - assessment of outcome (independent blind assessment or linked records = 1 star), sufficient duration of follow-up (≥3 months = 1 star), adequate follow-up of cohorts (≤30% of subjects lost to follow-up = 1 star). The maximum possible NOS rating was 9 stars.

Statistical Analysis

To measure the pooled aORs or aHRs, we divided the studies into 4 subgroups depending on the predictors during pregnancy that were listed in the article: PM, maternal parasitemia, maternal clinical malaria, or PAM. We then pooled the adjusted effect sizes of the predictor variable in each of the 4 subgroup analyses to determine their relative impact on the outcome variables in young children: parasitemia or clinically defined malaria. We performed meta-analyses using the inverse variance method, which assigns weight to each study according to the respective standard error for each of aOR or aHR rather than according to sample size alone. We then generated forest plots to display each adjusted estimate (aOR or aHR) and 95% confidence intervals (CIs). A two-tailed $P < .05$ was considered statistically significant.

We used prespecified random-effects meta-regression models and accounted for substantial heterogeneity between studies. This model estimates the between-study variances of effect sizes using the DerSimonian and Laird method [23], and it is added to within-study error to calculate total variance in the included studies. We then confirmed the heterogeneity between studies with Cochran's Q statistic (χ^2 test) and Higgins' I^2 statistic, $100\% \times (Q - \text{df})/Q$ where Q is Cochran's heterogeneity statistic and df is the degrees of freedom [24]. Higgins' I^2 statistic describes the ratio of heterogeneity to total variance, and the levels of 25%, 50%, and 75% indicate low, moderate, and high heterogeneity [24]. We defined substantial heterogeneity between studies as Higgins' I^2 statistic ≥50%.

We assessed publication bias using funnel plots and tested funnel plot asymmetry using Begg and Mazumdar's rank correlation test [25] and Egger's linear regression test [26]. We performed statistical analyses using Review Manager version 5.3.5 (Nordic Cochrane Centre, Copenhagen, Denmark) and STATA version 15.1 (StataCorp, College Station, TX).

RESULTS

Selection of Studies

A search of the medical literature using the defined thesaurus terms identified 2053 unique relevant articles. The initial screen found that 204 articles were eligible (Figure 1). We then conducted full-text reviews of these articles and excluded 180 reports because predictors, outcomes, follow-up periods, and/or study designs did not meet our inclusion criteria. Of the 24 remaining articles, 6 articles [27–32] were excluded because they are secondary analyses of datasets already included [19, 20, 33, 34]. We included 2 articles obtained from the Mother-Offspring Malaria Study Project because these reports used different predictors and outcomes [12, 35]. Ultimately, 19 articles met our inclusion criteria for the systematic review, and 11 of these had the requisite data for meta-analyses (Table 1): 9 studies reported aORs [11–14, 19, 33–36] and 4 studies reported aHRs [13, 20, 34, 37]; 2 of these studies reported both aORs and aHRs [13, 34]. Studies with different estimates of risk (aOR vs aHR) could not be analyzed together because HR is a measure of time-to-event outcomes, whereas OR is a measure of dichotomous outcomes regardless of timing. Eight articles were excluded from the meta-analyses because these studies only provided estimates of numbers of episodes [38], proportions [39], prevalence [10], RR [40], rate ratio [41], unadjusted measures [42], or results based on different classifications of the predictor [43] or outcome [44] variables that precluded pooling the effect sizes. Interrater agreement for selection of articles was near perfect (Cohen's kappa coefficient = 0.88). The Higgins' I^2 statistic was >50%, which indicated substantial heterogeneity between studies and stipulated the need for a random-effects meta-regression approach (Figures 2 and 3).

Malaria During Pregnancy Increased the Risk of Parasitemia in Young Children

Six eligible articles were used to estimate the pooled effects of malaria infection during pregnancy on *P falciparum* parasitemia of young children (Table 1). Subgroup analyses and total effect sizes are shown in Figure 2 [11, 13, 14, 20, 33, 35]. Based on the available data, the pooled aOR was 1.94 (95% CI, 0.93–4.07, $P = .08$) and the pooled aHR was 1.46 (95% CI, 1.07–2.00, $P < .001$). We identified a publication bias in the meta-analysis for estimating the pooled aOR of parasitemia (P value of Begg and Mazumdar's test = .09; P value of Egger's test = .023), but we did not identify bias for estimating pooled aHR (P value of Begg and Mazumdar's test = .55; P value of Egger's test = .14), indicating that the effect size calculation for aHR was more reliable.

Malaria During Pregnancy Increased the Risk of Clinical Malaria in Young Children

Eight articles reported the effects of malaria infection during pregnancy on clinical malaria of young children (Table 1). Subgroup analyses and total effect sizes are shown in Figure 3 [12–14, 19, 20, 34, 36, 37]. The pooled aOR was 2.82 (95% CI, 1.82–4.38; $P < .001$), and the pooled aHR was 1.31 (95% CI, 0.96–1.79; $P = .09$). No publication bias was identified in these analyses (P values of Begg and Mazumdar's test for OR and HR = .27 and .71, respectively; P values of Egger's test for OR and HR = .61 and .43, respectively).

DISCUSSION

The results of the meta-analyses suggest that malaria infection during pregnancy is associated with a significantly increased risk of *P falciparum* parasitemia (aHR, 1.46; 95% CI, 1.07–2.00; $P < .001$) and clinically defined malaria (aOR, 2.82; 95% CI, 1.82–4.38; $P < .001$) in young children. Our findings are supported by the additional 8 studies we identified in the systematic review but that were excluded from the meta-analyses [10, 38–44]. To our knowledge, only 2 previous publications have reviewed the medical literature on this topic [45, 46]. The report

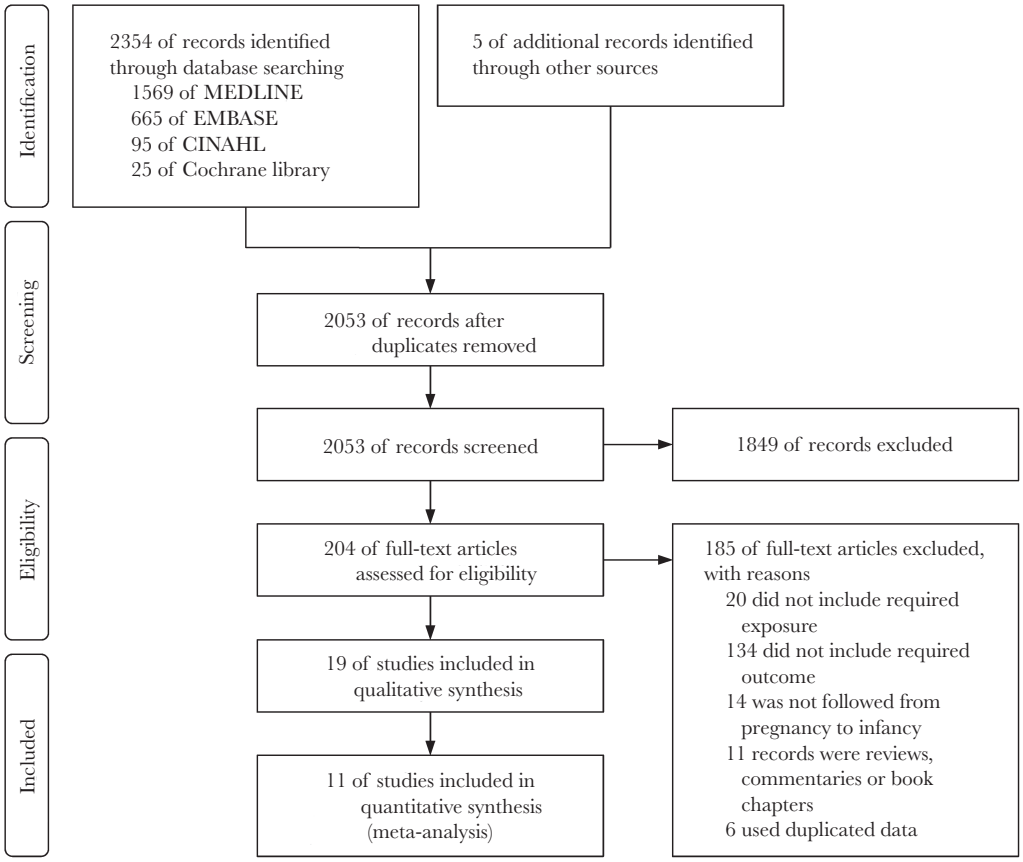

Figure 1. Study selection.

by Moya-Alvarez et al [45] concluded that PAM is associated with congenital malaria and early development of infant malaria. However, that report may have been biased in study selection, interpretation, and conclusions due to methodological limitations and nonstandardized analysis [47]. The systematic review by Kakuru et al [46] did find an association between malaria in pregnancy and malaria in infancy in some studies, but they did not perform a meta-analysis. To avoid similar potential deficiencies in our analyses, we used explicitly prespecified methods that complied with evidence-based standards (PRISMA and MOOSE) to enhance quality and transparency. For the meta-analyses, we adjusted the pooled effects for differences in sample size, study heterogeneity, and variance, and we assessed the studies for publication bias and study quality.

Although our meta-analyses concluded that malaria during pregnancy increases a young child's risk of acquiring malaria, the precise mechanism of elevated risk remains unclear. It has been postulated that certain infants exposed to *P falciparum* antigens in utero undergo prenatal immune priming that can lead to an immune tolerant phenotype after birth, and the altered immunological state could potentially be associated with an increased risk of acquiring malaria [10]. In addition, shared environmental and entomological exposures may partly explain the similar risks of malaria experienced by mothers and their offspring. However, the relatively lower risk for infants of primigravid women compared with higher risk for infants of multigravid women suggests that other mechanisms are also implicated [35].

It is interesting to note that although there were trends toward significance in the associations between malaria during pregnancy and the odds of parasitemia (pooled aOR = 1.94, P = .08) or hazard of clinical malaria (pooled aHR = 1.31, P = .09) in young children, they did not achieve statistical significance. On the other hand, the associations between malaria during pregnancy and hazard of parasitemia (aHR = 1.46) or odds of clinical malaria (aOR = 2.82) were highly significant (each $P < .001$). These discrepancies may be partially explained by publication bias that we detected in the analysis of aOR for parasitemia in children, the small number of eligible studies leading to low power (type 2 error), and potentially additional confounders that may not have been measured.

Similarly, in our subgroup analyses, we found that PM significantly increased the odds of clinical malaria, but not *P falciparum* parasitemia, in young children. A possible explanation for this discrepancy is that fewer studies with parasitemia as the outcome were available for inclusion, thereby limiting the power of the analysis. Alternatively, it is possible that differential expansion and differentiation of infants' regulatory T cells,

Table 1. Studies Included in the Systematic Review and Meta-Analyses[a]

Study	Study Site	Study Design	n	Follow-Up Period	Maternal Malaria Type	Outcome of Offspring	Measure of Effect	Unadjusted Effect	Adjusted Effect	Factors Adjusted for	NOS, Stars
Studies Included in Systematic Review and Meta-Analyses											
Asante et al [14]	Ghana	Cohort	1855	12 mo	PM	First parasitemia	HR (multigravidae)	1.06 (0.91–1.23)	1.02 (0.88–1.19)	Wealth index, thatched roof, residence area, and distance from health facility	8
					PM	First clinical malaria	HR (multigravidae)	1.08 (0.91–1.27)	1.01 (0.85–1.20)	Wealth index, thatched roof, residence area, and distance from health facility	
					PM	All episodes of parasitemia	HR (multigravidae)	1.03 (0.89–1.19)	0.98 (0.85–1.12)	Wealth index, thatched roof, residence area, and distance from health facility, infant ITN use, malaria exposure score	
					PM	All episodes of clinical malaria	HR (multigravidae)	1.00 (0.86–1.17)	0.94 (0.81–1.10)	Wealth index, thatched roof, residence area, and distance from health facility, infant ITN use, malaria exposure score	
Bardají et al [37]	Mozambique	RCT	997	12 mo	PM (acute)	Clinical malaria	OR	4.20 (1.94–9.12)	4.63 (2.10–10.24)	HIV status, malaria during pregnancy, and maternal mid-upper arm circumference	7
					PM (chronic)	Clinical malaria	OR	3.82 (2.06–7.08)	3.95 (2.07–7.55)	HIV status, malaria during pregnancy, and maternal mid-upper arm circumference	
					Clinical malaria	Clinical malaria	OR	2.40 (1.45–3.98)	1.96 (1.13–3.41)	HIV status, PM, and maternal mid-upper arm circumference	
Borgella et al [13]	Benin	Cohort	194	12 mo	PAM (1st trimester)	Parasitemia	OR	1.33 (0.36–4.94)	1.12 (0.23–5.45)	PM, age, distance from lake, bednet use, and birth season	9
					PAM (1st trimester)	Clinical malaria	OR	1.19 (0.35–4.08)	0.83 (0.13–5.18)	PM, age, distance from lake, bednet use, and birth season	
					PAM (2nd trimester)	Parasitemia	OR	1.14 (0.58–2.23)	0.87 (0.35–2.09)	PM, age, distance from lake, bednet use, and birth season	
					PAM (2nd trimester)	Clinical malaria	OR	1.24 (0.61–2.52)	0.81 (0.31–2.12)	PM, age, distance from lake, bednet use, and birth season	
					PAM (3rd trimester)	Parasitemia	OR	2.77 (1.49–5.15)	4.16 (1.64–10.54)	PM, age, distance from lake, bednet use, and birth season	

Table 1. Continued

Study	Study Site	Study Design	n	Follow-Up Period	Maternal Malaria Type	Outcome of Offspring	Measure of Effect	Unadjusted Effect	Adjusted Effect	Factors Adjusted for	NOS, Stars
					PAM (3rd trimester)	Clinical malaria	OR	2.80 (1.45–5.42)	4.61 (1.70–12.45)	PM, age, distance from lake, bednet use, and birth season	
					PM	Parasitemia	OR	1.58 (0.75–3.32)	0.72 (0.25–2.11)	PAM, age, distance from lake, bednet use, and birth season	
					PM	Clinical malaria	OR	1.53 (0.70–3.34)	0.59 (0.18–1.88)	PAM, age, distance from lake, bednet use, and birth season	
					PAM (1st trimester)	First parasitemia	HR	1.30 (0.57–2.92)	1.00 (0.42–2.39)	PM, age, distance from lake, bednet use, and birth season	
					PAM (1st trimester)	First clinical malaria	HR	1.44 (0.49–4.19)	0.97 (0.32–2.92)	PM, age, distance from lake, bednet use, and birth season	
					PAM (2nd trimester)	First parasitemia	HR	1.27 (0.73–2.19)	1.14 (0.62–2.12)	PM, age, distance from lake, bednet use, and birth season	
					PAM (2nd trimester)	First clinical malaria	HR	1.35 (0.74–2.47)	1.15 (0.58–2.28)	PM, age, distance from lake, bednet use, and birth season	
					PAM (3rd trimester)	First parasitemia	HR	2.23 (1.36–3.65)	2.95 (1.58–5.50)	PM, age, distance from lake, bednet use, and birth season	
					PAM (3rd trimester)	First clinical malaria	HR	2.26 (1.29–3.96)	3.19 (1.59–6.38)	PM, age, distance from lake, bednet use, and birth season	
					PM	First parasitemia	HR	1.41 (0.79–2.52)	0.68 (0.34–1.38)	PAM, age, distance from lake, bednet use, and birth season	
					PM	First clinical malaria	HR	1.33 (0.69–2.54)	0.60 (0.28–1.32)	PAM, age, distance from lake, bednet use, and birth season	
Boudová et al [20]	Malawi	RCT	473	1 y	PM	Parasitemia	OR	2.7(1.1–6.7)	2.5 (1.0–6.3)	Age, GA, and clinical trial arm	6
					PM	Clinical malaria	OR	4.1 (1.3–13.1)	3.9 (1.2–13.0)	Age, GA, and clinical trial arm	
					Parasitemia	Parasitemia	OR	1.5 (0.5–4.4)	1.5 (0.5–4.4)	Age, GA, and clinical trial arm	
					Parasitemia	Clinical malaria	OR	1.5 (0.3–7.3)	1.4 (0.3–7.0)	Age, GA, and clinical trial arm	
				2 y	PM	Parasitemia	OR	2.6 (1.0–6.6)	2.8 (1.1–7.5)	Age, GA, and clinical trial arm	
					PM	Clinical malaria	OR	2.8 (1.0–7.9)	3.2 (1.1–9.4)	Age, GA, and clinical trial arm	
					Parasitemia	Parasitemia	OR	1.4 (0.5–3.8)	1.5 (0.6–4.1)	Age, GA, and clinical trial arm	

Table 1. Continued

Study	Study Site	Study Design	n	Follow-Up Period	Maternal Malaria Type	Outcome of Offspring	Measure of Effect	Unadjusted Effect	Adjusted Effect	Factors Adjusted for	NOS, Stars
					Parasitemia	Clinical malaria	OR	1.3 (0.4–4.4)	1.5 (0.4–4.9)	Age, GA, and clinical trial arm	
					PM	Cum. parasitemia	RRR	1.6 (1.0–2.6)	NA	NA	
					PM	Cum. clinical malaria	RRR	2.3 (1.1–4.8)	NA	NA	
					Parasitemia	Cum. parasitemia	RRR	1.4 (0.8–2.4)	NA	NA	
					Parasitemia	Cum. clinical malaria	RRR	2.1 (1.0– 4.5)	NA	NA	
Gonçalves et al [12]	Tanzania	Cohort	882	4 y	PM (1st delivery)	First clinical malaria	HR	NA	1.12 (0.44–2.82)	Hgb genotype, bednet use, sex, village of residence, and season	9
				4 y	PM (1st delivery)	Parasite density	Coefficient	NA	0.16 (−0.20 to 0.52)	Hgb genotype, bednet use, sex, village of residence, and season	
Le Port et al [33]	Benin	Cohort	545	18 mo	PM	First parasitemia	HR	1.59 (1.17–2.16)	1.57 (1.16–2.14)	Exposure prediction	9
Mutabingwa et al [35]	Tanzania	Cohort	453	54 wk	PM	First parasitemia	HR	1.33 (0.97–1.83)	1.41 (1.01–1.99)	Residence area, birth season, gravidity, and bednet use	9
Ndibazza et al [19]	Uganda	RCT	2289	5 y	PAM	All episodes of clinical malaria	HR	NA	1.23 (1.01–1.51)	Age, parity, education, bednet ownership, SES, HIV status, and residence area	8
					PAM	All episodes of asymptomatic malaria	HR	NA	1.27 (0.83–1.97)	Age, parity, education, bednet ownership, SES, HIV status, and residence area	
Schwarz et al [36]	Gabon	RCT	527	30 mo	PM	First clinical malaria	HR	2.3 (1.3–3.9)	2.1 (1.2–3.7)	Gravidity, residence area, birth season, preventive treatment, and bednet use	7
Sylvester et al [34]	Tanzania	Cohort	206	24 mo	PM	Clinical malaria	OR	4.632 (2.248–9.541)	4.791 (2.21–10.38)	Gravidity, birth weight, age, and birth season	9
Tassi Yunga et al [11]	Cameroon	Cohort	72	12 mo	PM (PM + High)	First parasitemia	HR	1.5 (0.8–2.8)	1.5 (0.7–3.1)	Residence area, gravidity, birth season, Hgb genotype, and cord MSP1 IgG level	7
					PM (PM + Low)	First parasitemia	HR	2.6 (1.3–4.8)	2.8 (1.3–6.0)	Residence area, gravidity, birth season, Hgb genotype, and cord MSP1 IgG level	

Table 1. Continued

Study	Study Site	Study Design	n	Follow-Up Period	Maternal Malaria Type	Outcome of Offspring	Measure of Effect	Unadjusted Effect	Adjusted Effect	Factors Adjusted for	NOS, Stars
Studies Included in Systematic Review but Not Meta-Analyses											
Awine et al [41]	Ghana	RCT	686	12 mo	PM	Clinical malaria	Rate ratio	NA	0.86 (0.54–1.37)	Age, parasitemia status at enrolment, Hgb, birth season, sex, SES, residence area, irrigated area, and ITN use	8
Bonner et al [39]	Kenya	Case Control	100	12 mo	PM	Parasitemia	Proportion	15.6% in PM+ and 14.7% in PM–	NA	NA	6
						Clinical malaria	Proportion	3.6% in PM+ and 1.4% in PM–	NA	NA	
Cot et al [44]	Cameroon	Cohort	79	2 y	PM	High, medium, and low density parasitemia	OR	NA	2.3 (0.38–14), 2.6 (0.46–15), and 0.4 (0.05–2.90)	2H3 chondroitin sulfate, gravidity, and residence area	6
					PM	High, medium, and low density parasitemia	OR	NA	2.6 (0.39–17), 2.8 (0.50–16), and 0.4 (0.05–3.4)	Palo Alto chondroitin sulfate, gravidity, and residence area	
De Beaudrap et al [40]	Uganda	RCT	832	12 mo	Parasitemia	First parasitemia	RR	NA	2.97 (1.37–6.42)	Education, age, gravidity, residence area, season, HIV status, and bednet use	8
					PM	First parasitemia	RR	NA	10.42 (2.64–41.10)	Education, age, gravidity, residence area, season, HIV status, and bednet use	
Le Hesran et al [43]	Cameroon	Cohort	197	2 y	PM	Parasitemia	Prevalence	Higher in PM+ between 5 and 8 mo	NA	NA	6
					PM	Clinical malaria	Prevalence	46.5% in PM+ and 38.5% in PM–	NA	NA	
Malhotra et al [10]	Kenya	Cohort	586	3 y	PAM	Parasitemia	RR	Exposed/sensitized: 1.4 (0.97–2.07), not exposed: 1.61 (1.10–2.43)	NA	NA	9
Mutabingwa et al [38]	Tanzania	CT	327	1 y	Parasitemia	Parasitemia	N (episodes)	3–5 vs 6–7 median no. of parasitemia episodes in infants of mothers who had no parasitemia vs 2+ episodes of parasitemia, respiratory	NA	NA	7
Slutsker et al [42]	Malawi	RCT	3915	3 mo	Parasitemia	Parasitemia	OR	1.1 (0.7–1.9)	NA	NA	6
					PM	Parasitemia	OR	1.2 (0.9–1.4)	NA	NA	

Abbreviations: Cum., cumulative; CT, clinical trial (not randomized); GA, gestational age at delivery; Hgb, hemoglobin; HIV, human immunodeficiency virus; HR, hazard ratio; IgG, immunoglobulin G; ITN, insecticide-treated bed net; mo, months; n, number; NA, not applicable; NOS, Newcastle-Ottawa quality scale; OR, odds ratio; PAM, pregnancy-associated malaria; PM, placental malaria; PM+/–, PM positive/negative group; RCT, randomized controlled trial; RR, relative risk; RRR, relative rate ratio; SES, socioeconomic status; wk, weeks; y, years.
[a]Age and HIV status refer to maternal age and HIV status.

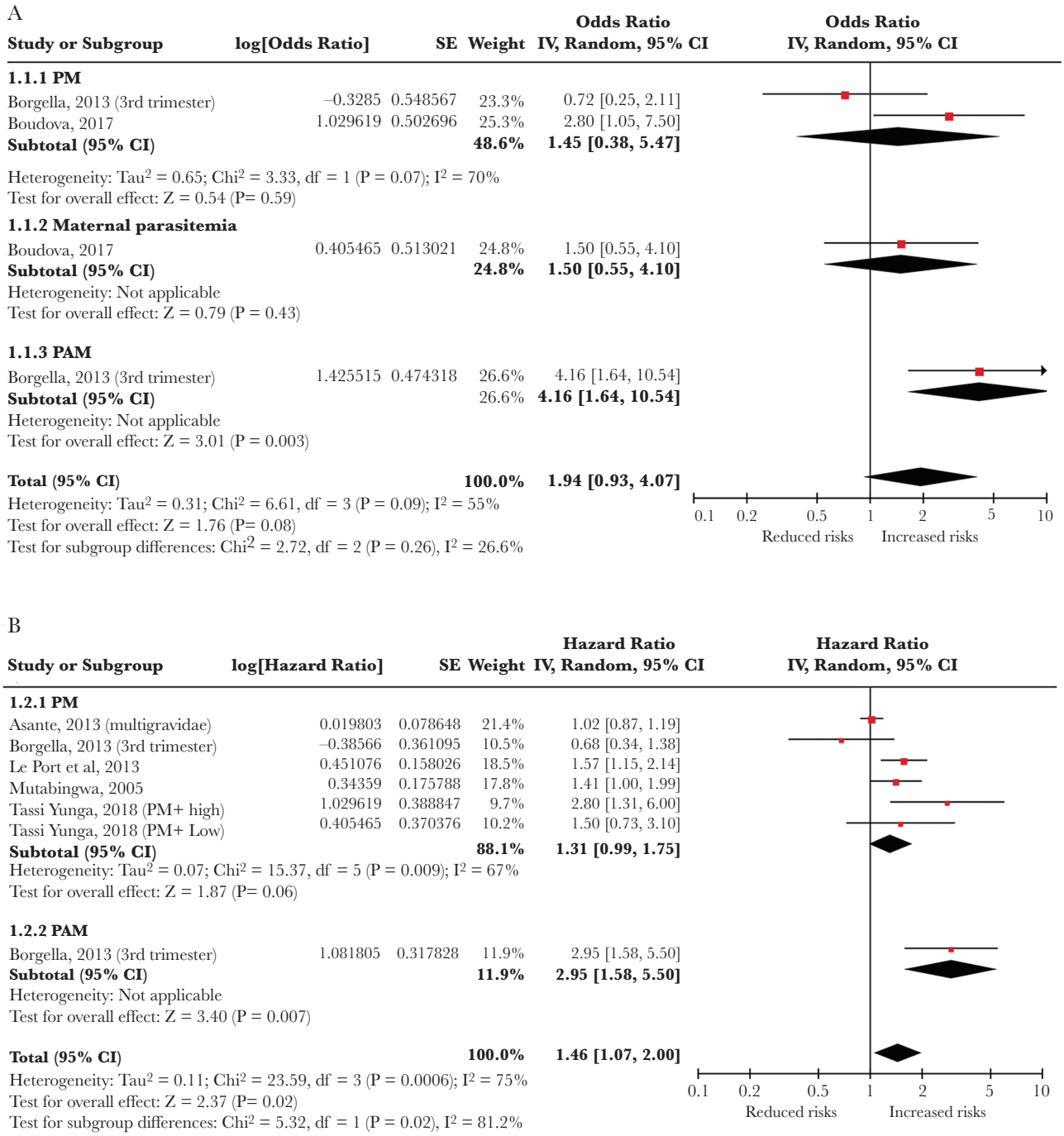

Figure 2. Forest plots summarizing the pooled analyses of adjusted (A) odds ratios and (B) hazard ratios from studies assessing the relationship between malaria infection during pregnancy and parasitemia of young children. CI, confidence interval; IV, intravenous; PM, placental malaria.

effector memory cells, and dendritic cells in the presence of PM may lead to increased levels of suppressive cytokines and/or enhanced effector functions that inhibit parasite replication [48]. We could not evaluate associations between other subgroups of maternal malaria infection (parasitemia, clinical malaria, and PAM) and risk of malaria in young children because the analyses were limited by a small number of studies.

Two studies that investigated the effect of timing of malaria infection during pregnancy on the risk of malaria in the progeny confirmed that a temporal association existed [13, 40]. It is known that B- and T-cell repertoire diversity and complexity in human fetuses mature as the pregnancy advances [49]. Therefore, the responses of the fetal immune system to malaria antigens may differ depending on the timing of the

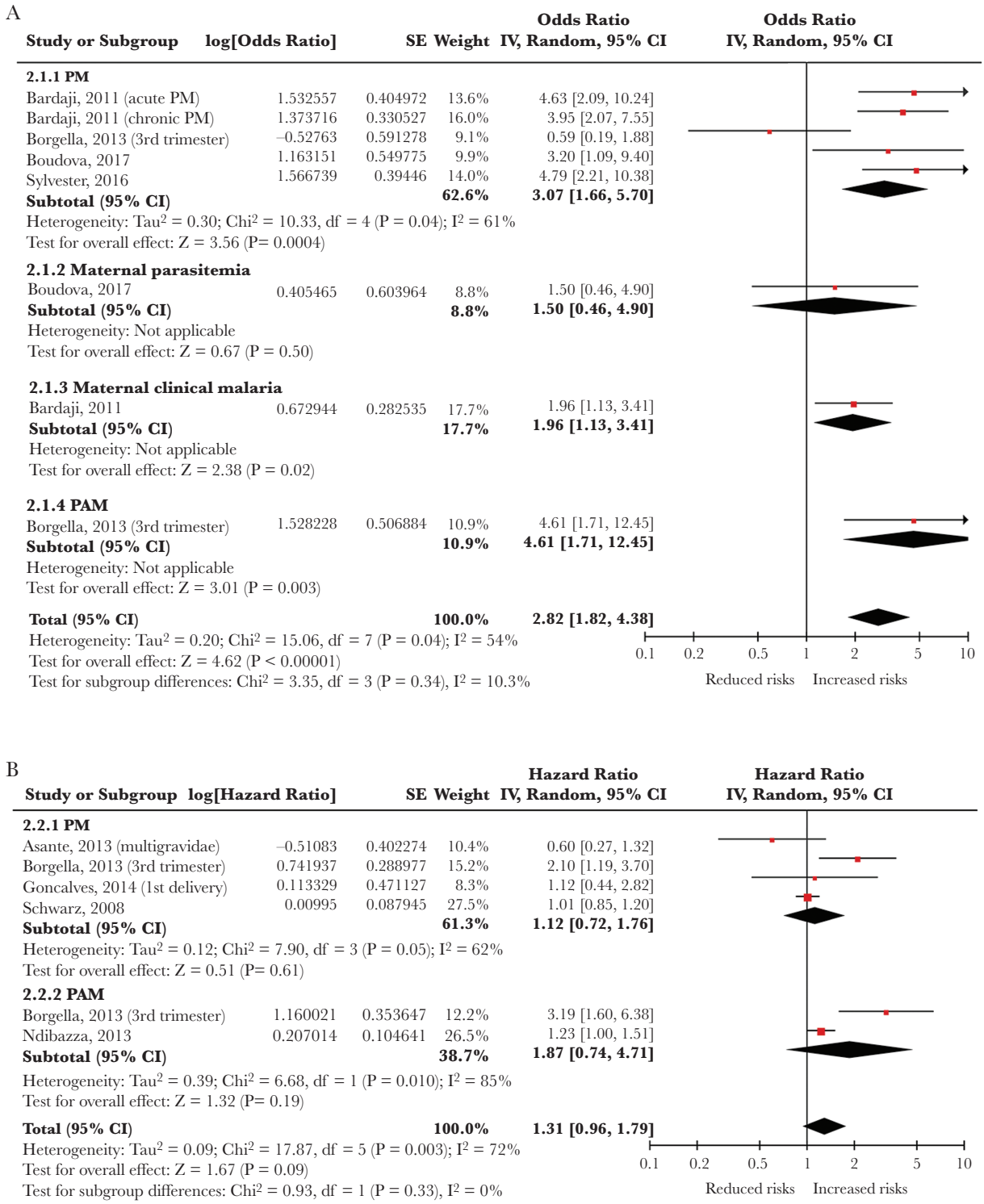

Figure 3. Forest plots summarizing the pooled analyses of adjusted (A) odds ratios and (B) hazard ratios from studies assessing the relationship between malaria infection during pregnancy and clinically defined malaria of young children. CI, confidence interval; IV, intravenous; PM, placental malaria.

maternal malaria infection. More immuno-epidemiological studies are needed to elucidate how temporal or other factors related to maternal malaria infections contribute to the risk of malaria in young children.

There is strong evidence that a woman's susceptibility to malaria is greatest in her first pregnancy, and her risk of malaria infection decreases with successive pregnancies, likely due to the development of naturally acquired immunity that blocks

parasite adherence in the placenta [5]. In contrast to this observation, the progeny of primigravid women have the lowest risk of acquiring malaria, particularly if PM is absent [14, 35], compared with the young children of multigravid women [19]. We were not able to perform subgroup meta-analyses to examine whether malaria infection of young children is modified by the interaction between malaria infection during pregnancy and gravidity because of the small number of studies and the heterogenous classification of predictor variables, definitions of outcomes, and statistical tests [12, 14, 35]. Mutabingwa et al [35] reported that infants of primigravid women had significantly lower odds of parasitemia if they had PM (aOR, 0.21; 95% CI, 0.09–0.47) or did not have PM (aOR, 0.67; 95% CI, 0.50–0.92) compared with multigravid women who did not have PM; Gonçalves et al [12] demonstrated that infants of multigravid women with PM had significantly higher hazard of moderately severe or severe malaria (aHR, 1.67; 95% CI, 1.25–2.22) compared with primigravid women with no PM. However, these 2 reports [12, 35] derived data from the same Tanzanian cohort. Asante et al [14] found that infants of primigravid women had a significantly lower hazard of clinical malaria (aHR, 0.60; 95% CI, 0.43–0.84) and parasitemia (aHR, 0.64; 95% CI, 0.48–0.86) if they had no PM compared with multigravid women who also had no PM. Carefully designed studies evaluating the influence of complex interactions between maternal malaria and gravidity on childhood malaria are needed.

A strength of our study is that the analyses were performed using large-scale data derived from 7611 subjects residing in several sub-Saharan African countries. However, our study has several limitations: we did not perform meta-analyses for all predictor subgroups because of insufficient numbers of eligible studies and inconsistent stratification methods among articles; we detected some publication bias that invariably affected the results; many contributing studies may be confounded by shared maternal and infant exposure to infectious mosquitoes, which may not be completely accounted for by adjustment for bed net use, seasonality, and distance to lakeshores; we did not investigate the influence of the precise timing of maternal malaria infection, which was highly variable, or whether there was a potential dose-response effect of maternal parasite densities because of limited data; we did not include duration of follow-up or timing of testing of infants as a covariate in the analyses due to insufficient numbers of studies; and diagnostic tests for malaria (microscopy, RDT, and PCR assays) had different sensitivities. Finally, we did not specifically evaluate the impact of maternal intermittent preventive treatment in pregnancy because of inconsistent reporting although most of the studies incorporated this practice as standard of care.

CONCLUSIONS

In conclusion, the results of our systematic review and meta-analyses showed that malaria infection during pregnancy increases the overall risk of malaria in young children. Despite the heterogeneity of specific predictors, the increased risk of malaria in young children was reasonably consistent. Our findings also revealed knowledge gaps about how risk-modifying factors in pregnancy interact to affect offspring, including the impact of the precise timing of malaria infection, gravidity, parasite density, PM, and intermittent preventive treatment in pregnancy. Therefore, to design highly effective interventions, carefully designed future studies that control for potential confounding by shared exposure of mothers and infants to infectious mosquitoes are urgently needed to elucidate the precise mechanisms by which malaria during pregnancy impacts young children.

Notes

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