JMCH Journal of Maternal and Child Health (2020), 05(05): 549-562
Masters Program in Public Health, Universitas Sebelas Maret

Research

Meta-Analysis: The Effect of Malaria Infection on the Incidence of Low Birth Weight

Feri Yuda Anggara[1], Setyo Sri Rahardjo[2], Bhisma Murti[1]

[1]Masters Program in Public Health, Universitas Sebelas Maret
[2]Faculty of Medicine, Universitas Sebelas Maret

ABSTRACT

Background: Malaria is a parasitic infectious disease. Malaria contributes to morbidity and mortality in high-risk groups, namely pregnant women and children under five. Malaria infection during pregnancy can adversely affect both the mother and the fetus, including maternal anemia, miscarriage, preterm labor, intrauterine growth retardation, and the delivery of infants with low birth weight (LBW). This study aims to analyze the magnitude of the influence of malaria infection on the incidence of LBW by a meta-analysis study.

Subjects and Method: This was a systematic review and meta-analysis conducted by following the PRISMA flow diagram. The process of searching for articles is carried out through a journal database which includes: PubMed, Springer Link, Google Scholar and Science Direct by selecting articles published in 2000-2020. Keywords used include: "Malaria infection AND low birth weight", "malaria during pregnant "AND" low birth weight", "malaria during pregnant AND low birth weight AND adjusted ratio". The inclusion criteria were full paper articles with observational study design, articles using English, multivariate analysis used with adjusted odds ratio. Articles that meet the requirements are analyzed using the Revmen5.3 application.

Results: Thirteen articles were reviewed in this study with a cohort and cross-sectional study design. Meta-analysis of 4 cohort studies showed that pregnant women with malaria infection had a 1.31 times increased risk of low birth weight compared with those without malaria infection (aOR= 1.31; 95% CI= 0.90 to 1.90; p= 0.15). A meta-analysis of 9 cross-sectional studies showed that pregnant women with malaria infection had a 2.11 times increased risk of low birth weight compared with those without malaria infection (aOR= 2.11; 95% CI= 1.33 to 3.33; p= 0.001).

Conclusion: Malaria infection increases the risk of low birth weight.

Keywords: malaria infection, low birth weight

Correspondence:
Feri Yuda Anggara. Masters Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: feriyudha90@gmail.com. Mobile: 085-220426805.

Cite this as:
Anggara FY, Rahardjo SS, Murti B (2020). Meta-Analysis: The Effect of Malaria Infection on the Incidence of Low Birth Weight. J Matern Child Health. 05(05): 549-562. https://doi.org/10.26911/thejmch.2020.-05.05.09.

BACKGROUND

Malaria is a life-threatening infectious parasitic infection and poses a significant global health threat (Buck and Finnigan, 2019). Malaria contributes to morbidity and mortality, especially in high-risk groups, namely pregnant women and children under five. In 2018, approximately 11 million pregnancies in sub-Saharan Africa with moderate and high transmission countries were affected by malaria infection (WHO, 2019).

Malaria infection during pregnancy can adversely affect the mother and the fetus, including maternal anemia, miscarriage, preterm delivery, intrauterine growth retardation, and the delivery of infants with low birth weight are risk factors for causing death (CDC, 2020).

Eleven million pregnant women who were exposed to malaria infection in 2019 gave birth to around 872 thousand children with low birth weight. 16% of all children with low birth weight are in African countries (WHO, 2019). The number of malaria cases in pregnant women in Indonesia in 2019 was 1,769. Most cases were reported from Papua province. The highest number of pregnant women screened for malaria was reported from East Nusa Tenggara Province as much as 61,065, while the total number of pregnant women screened in 2018 was 355,956 (Ministry of Health, 2019).

Malaria infection during pregnancy is a substantial health risk for pregnant women and their fetuses and babies. Pregnant women in high transmission areas are at risk of experiencing decreased immunity due to parasites that will attack the placenta (CDC, 2020). The body's natural immune response to malaria involves both antibody-mediated protection and a cytokine-mediated innate immune response. A placenta infected with malaria is characterized by the presence of red blood cells infected with plasmodium causing an inflammatory response that can disrupt the supply of nutrients from the mother-fetus and cause fetal growth restriction (Quanquin et al., 2020).

Malaria parasite infection in early pregnancy is associated with a delayed effect on fetal growth. Nearly 40% of these infections occur during the first half of pregnancy, and 18% occur before the 17th week of pregnancy. These infections can interfere with baseline development of the placenta and therefore reduce final capacity. for nutrient transport across the placenta (Briand et al., 2016).

There is a two-way interaction between nutrition and inflammation. Inflammation negatively impacts nutritional status and poor nutrition negatively impacts immune function. Potentially, decreased immune function due to malnutrition can increase the risk of placental malaria (Lawford et al., 2019). Nutritional deficiencies play a role in increasing the risk of malaria and poor birth outcomes and independently indicate the risk of poor neurodevelopmental outcomes. Pregnancy with malaria affects low birth weight (LBW) (Alvarez et al., 2014).

The risk of birth weight loss occurs with episodes of exposure to malaria either symptomatic or asymptomatic. The reduction in birth weight due to malaria cannot be separated from the condition of anemia in the mother (Rijken et al., 2012).

Meta-analysis is an epidemiological study that combines or combines statistically the results of a number of primary studies that can be combined, testing the same hypothesis in the same way, so as to obtain a quantitative overview (Huque, 1988; Greenhalgh, 1977; Last, 2001; Delgado- Rodriguez, 2001 in Murti 2018). Meta analysis is carried out by summarizing and synthesizing quantitatively the various estimates generated from various similar studies to make the most accurate estimate. This study aims to obtain conclusive conclusions about "The Effect of Malaria Infection on the Incidence of Low Birth Weight".

SUBJECTS AND METHOD

1. Study Design

This was a systematic review and meta-analysis carried out by following the PRISMA flow diagram. The process of searching for articles is carried out by searching through journal databases which include: PubMed, Springer Link, Google

Scholar and Science Direct. Keywords used include: Malaria infection AND low birth weight", "malaria during pregnant" AND "low birth weight", "malaria during pregnant AND low birth weight AND adjusted ratio".

2. Inclusion Criteria

The inclusion criteria for articles that can be reviewed are full paper articles with observational study design, articles in English, the analysis used is multivariate with adjusted odds ratios, the interventions given are those who have a history of malaria infection during pregnancy, the study subjects are pregnant women, the outcome was LBW.

3. Exclusion Criteria

Exclusion criteria for articles included primary articles published where meta-analysis was carried out and statistical results reported in the form of a bivariate analysis.

4. Operational definition of variables

The article search was carried out by considering the eligibility criteria defined using the PICO model. The population in the study were pregnant women with intervention in the form of malaria infection, the comparison was no malaria infection and the outcomes were LBW.

LBW is a baby with a birth weight of less than 2500 g. The instrument used is the weight scale

Malaria infection is a specific condition in pregnant women and is characterized by the accumulation of red blood cells containing the malaria parasite. The instruments used were the results of microscopic examination, RDT, PCR

5. Study instrument

The research stages followed the PRISMA flow diagram and the assessment of the quality of research articles using the Critical Appraisal Skills Program (CASP) for Cohort Study, Critical Appraisal Checklist for Cross-sectional Study (CEBMa, 2014).

6. Data Analysis

The data analysis process in this study was carried out using the Review Manager application (RevMen 5.3), to determine the effect size and heterogeneity of the study. The results of meta-analysis data processing are presented in the form of a forest plot and a funnel plot.

RESULTS

The process of searching for articles is carried out by searching through the database according to PRISMA. The flow diagram can be seen in Figure 1.

Research related to the effect of malaria infection on LBW consisted of 13 articles from the initial search process yielding 1462 articles. The research articles came from 3 continents, namely Asia, Africa and South America. Figure 2 shows the areas where articles were drawn according to the inclusion criteria. Furthermore, the researcher conducted an assessment of the quality of the articles (Tables 1 and 2). Table 3 shows that there are 4 cohort study articles and 9 cross-sectional study articles as evidence of the association of the effect of malaria infection on the incidence of LBW.

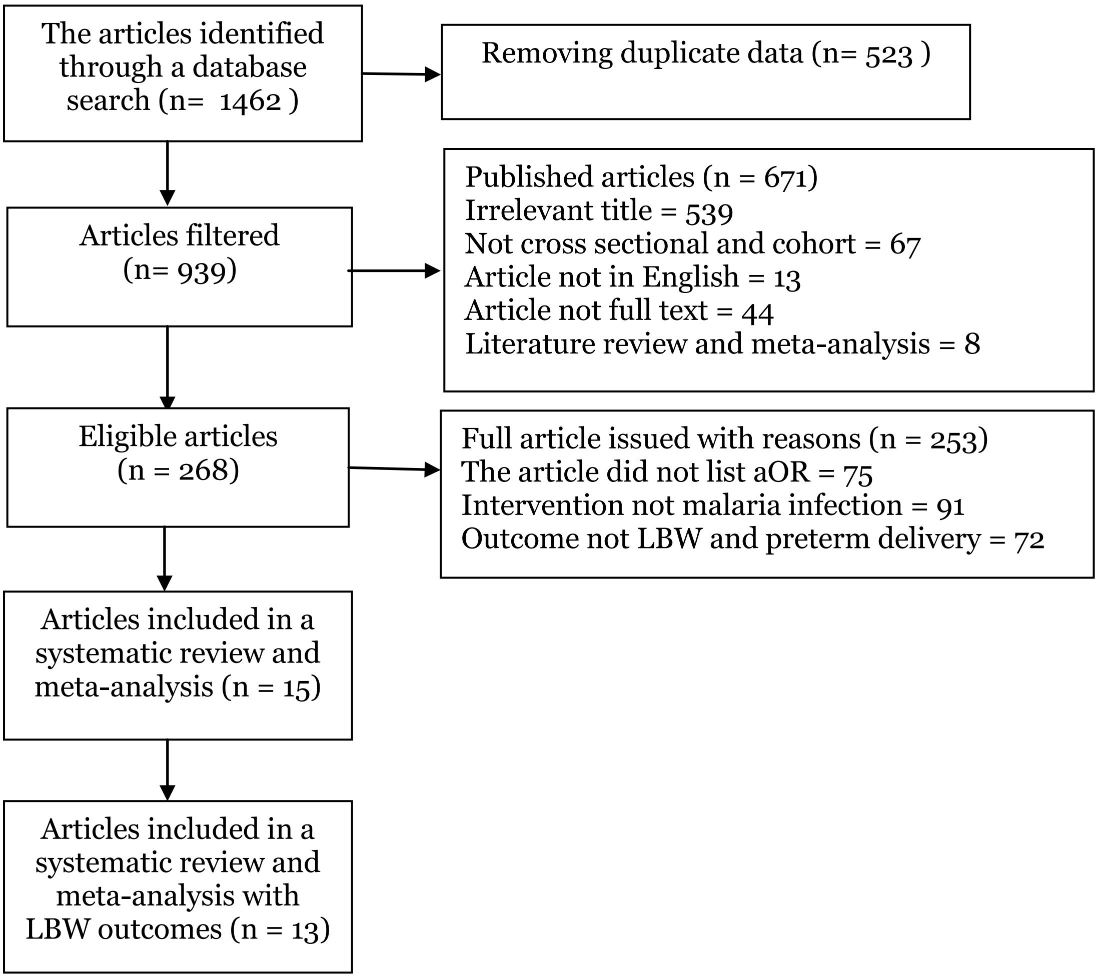

Figure 1. PRISMA flow diagram

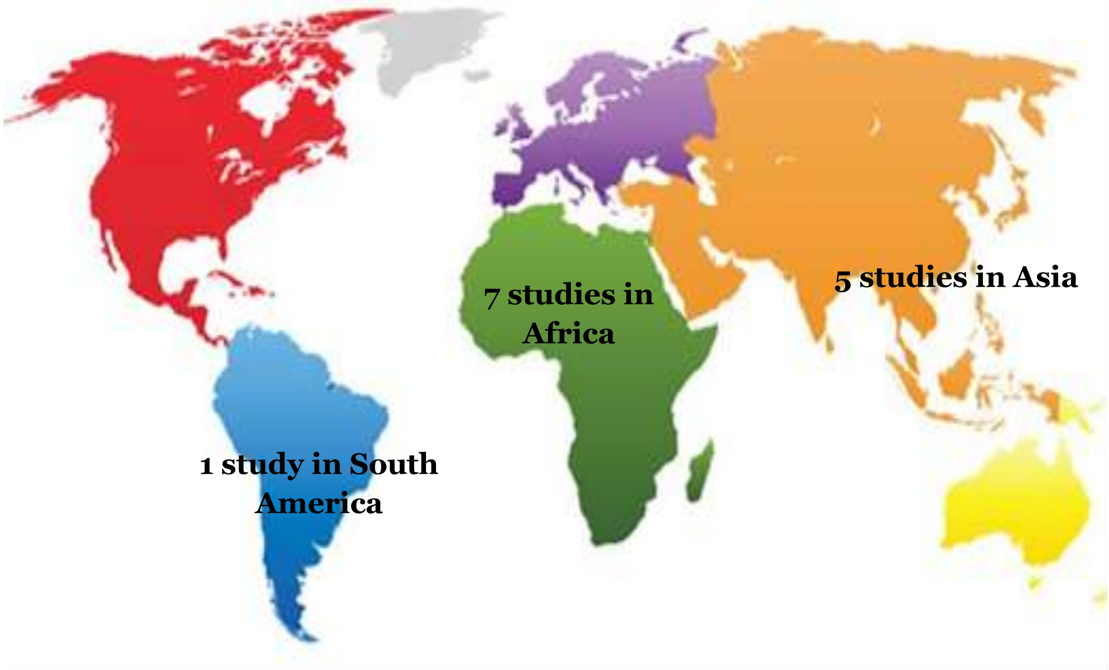

Figure 2. Map of the research area

Table 1. Assessment of Research Quality using the Critical Appraisal Skills Program for C

Checklist	PUBLI (Author	
	Unger et al. (2019)	Cottrell et al. (2015)
Does this research address clearly focused issues?	1	1
Was the group included in an acceptable way?	1	1
Is exposure measured accurately to minimize bias?	1	1
Are the results measured accurately to minimize bias?	1	1
Have the authors identified all the important confounding factors?	1	1
Was the follow-up to the subject of this study complete?	0	0
What are the results of this study?	1	1
How precise is the result?	1	1
Do you believe in the results?	1	1
Can the results be applied to the local population?	0	1
Are the results of this study consistent with other available evidence?	1	1
What are the implications of this study for practice?	1	1
Total	10	11

Note: Yes = 1, No= 0

Table 2. Assessment of Research Quality using the Critical Appraisal for Cross-sectional

Checklist	PUBLICATION (Author andYear)					
	Mahande et al. (2016)	Poepspo-prodjo et al. (2008)	Asundep et al. (2014)	Albiti et al. (2010)	Omer et al. (2019)	Brutus e al. (2013)

Does the sampling method create bias (selection)?	0	0	0	0	0	0
Does the research sample taken represent the designated population?	1	1	1	1	1	1
Was the sample size based on pre-study considerations?	1	1	1	0	1	1
Was a satisfactory response achieved?	1	1	1	1	1	1
Are the research instruments valid and reliable?	1	1	1	1	1	1
Is statistical significance assessed?	1	1	1	1	1	1
Are confidence intervals given for the main outcome?	1	1	1	1	1	0
Are there any confounding factors that have not been taken into account?	0	0	0	0	0	0
Are the results applicable to your research?	1	1	1	1	1	1
Total	10	10	10	9	10	9

Note: Yes = 1, No= 0

Table 3. Description of the primary study meta-analysis of the effect of malaria infection

Author (year)	Country	Study Design	Sample	P Population	I Intervention	
Unger et al.	Papua	Cohort	2,190	Pregnant	Peripheral blood microscopic	N

Author (year)	Country	Study Design	Sample	P Population	I Intervention	
Stanisic et al.(2015)	Papua New Guninea	Cohort	470	Pregnant women	Primigravida, smoking, education, use of mosquito nets, history of clinical symptoms, maternal HB, chronic infection parasitemia *, genotypes of SAO, CR1 and α + -thalassemia,	M ed hi ab in
Mahande et al. (2016)	Tanzania	Cross sectional	30,797	Pregnant women	Malaria infection *, worm infection, amoebic infection	Ne in
Poepspoprodjo et al (2008)	Indonesia	Cross sectional	3,046	Pregnant women	Malaria parasitemia infection *	Ne in
Asundep et al. (2014)	Ghana	Cross sectional	630	Pregnant women	Malaria infection *, worm infection	Ne in
Albiti et al. (2010)	Yaman	Cross sectional	900	Pregnant women	Placental malaria infection *	Ne
Ndeserua et al. (2015)	Tanzania	Cross sectional	350	Pregnant women	Placental malaria infection *	Ne
Omer et al. (2019)	Sudan	Cross sectional	1,149	Pregnant women	living in rural areas, low education, irregular ANC visits, use of mosquito nets, submicroscopic parasitemia *	Li ca in ne
Brutus et al. (2013)	Bolivia	Cross sectional	1,507	Pregnant women	Premature babies, babies with female sex, primiparous, mater-	Ne m

Author (year)	Country	Study Design	Sample	P Population	I Intervention	
					scopic malaria infections *, age of pregnant women <21 years, primigravida, C-reactive protein (CRP) level (CRP> 6 mg / L)	m pr m (C

*Variables entered in the meta-analysis

Forest plot

Interpretation of the results from the meta-analysis process can be seen through a forest plot. Figure 3 shows that malaria infection increases the incidence of LBW. The meta-analysis results of the cohort study showed that malaria infection could increase the incidence of LBW by 1.31 times compared to LBW incidence that was not affected by malaria infection (aOR= 1.31, 95% CI= 0.90-1.90, p= 0.15). The heterogeneity of the research data shows I2 = 0% so that the distribution of the data is declared homogeneous (fixed effect model). The results of the meta-analysis of cross-sectional studies showed that malaria infection increased the incidence of LBW by 2.11 times compared to the incidence of LBW that was not affected by malaria infection (aOR= 2.11, 95% CI= 1.33-3.33, p= 0.001). The heterogeneity of the research data shows I^2= 77% so that the distribution of the data is stated to be heterogeneous (random effect model).

Funnel Plot

A funnel plot is a plot that depicts the estimated effect size of each study on its estimate of accuracy which is usually the standard error. Figure 4 shows that there is a publication bias which is characterized by asymmetry of the right and left plots where 6 plots are on the right, 6 plots are on the left and 1 plot touches the line. The plot on the left of the graph appears to have a standard error between 0 and 0.8 and the plot on the right has a standard error between 0.4 and 1. A bias also occurs from an imbalance between the distances between studies on both the right and left of the funnel plot.

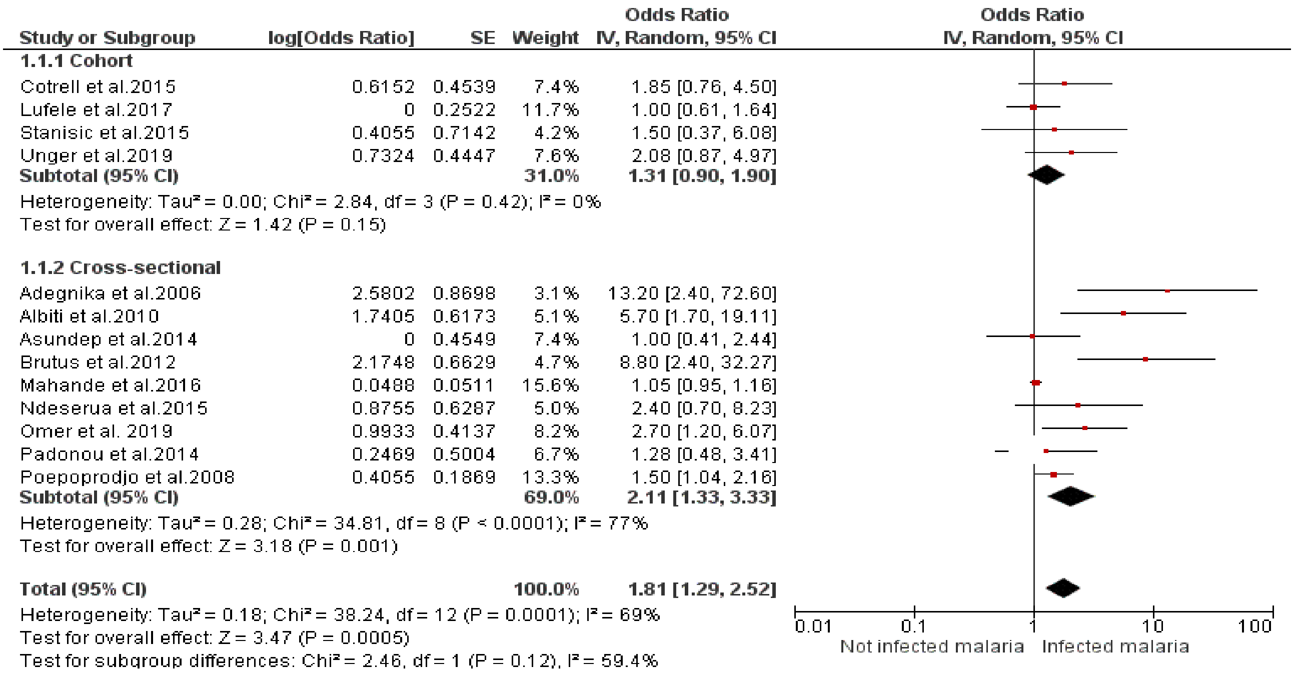

Figure 3. Forest plot of the effect of malaria infection on LBW

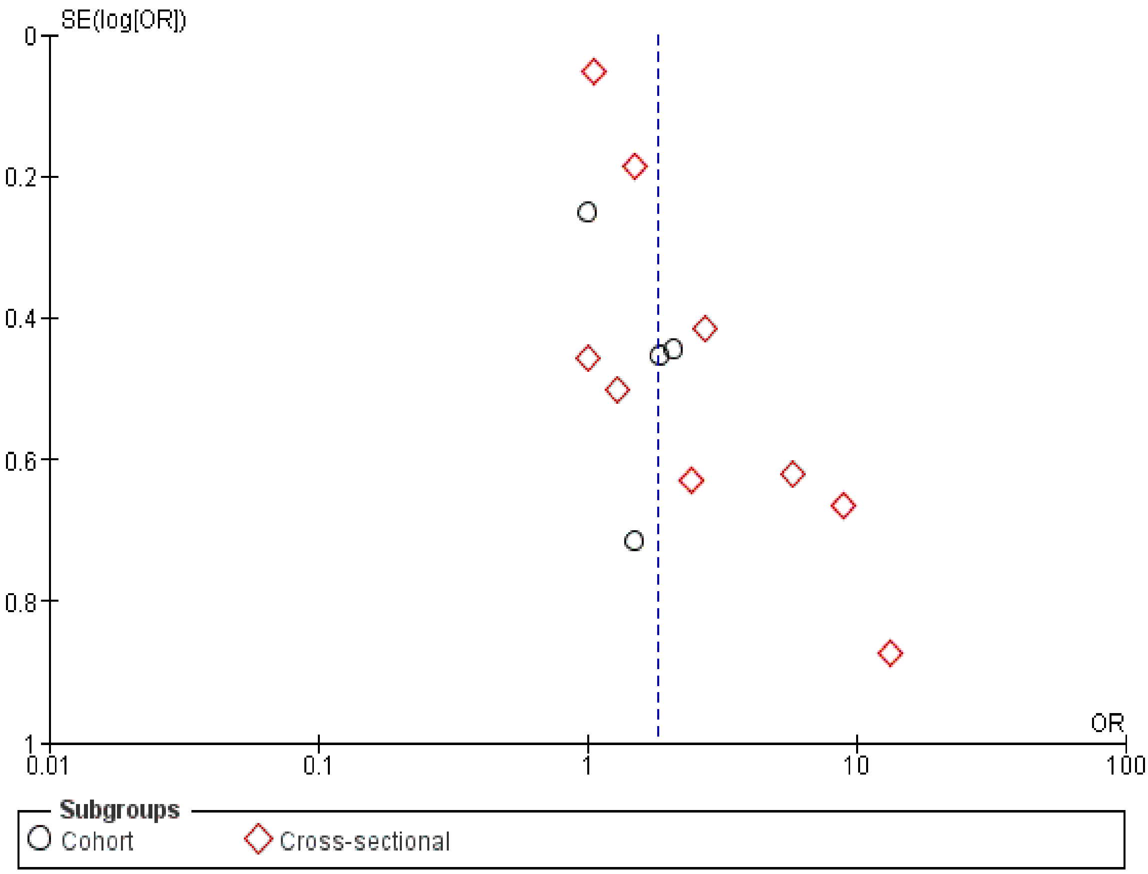

Figure 4.Funnel plot of the effect of malaria infection on LBW

DISCUSSION

This systematic review and meta-analysis research raises the theme of the effect of malaria infection on pregnant women. The independent variable analyzed was malaria infection. The dependent variable in this systematic review and meta-analysis is the incidence of LBW.

The results of the primary study carried out by a systematic study and meta-analysis show an epidemiological study design with a larger population sample, with different demographic characteristics in malaria endemic areas in different countries, thus providing a basis for concluding that malaria infection has a statistical effect on the incidence of birth weight. low.

Malaria is found mainly in climatic factors such as temperature, humidity and rainfall. Malaria is transmitted in tropical and subtropical areas, where the Anopheles mosquito can survive and breed, and the malaria parasite can complete the growth cycle in mosquitoes. Generally, malaria cases occur in warmer areas closer to the equator. The highest transmission rates are found in South Africa's Sahara and in parts of Oceania such as Papua New Guinea (CDC, 2020).

The results of the primary study analysis carried out by systematic review and meta-analysis show that studies that meet the analysis criteria are found in Africa (Benin, Gabon, Tanzania, Ghana, and Sudan), Asia (Indonesia, Papua New Guinea and Yemen), and America. South (Bolivia).

Snow and Guyat (2004) stated that malaria in pregnant women is related to the incidence of anemia in mothers, premature delivery, and newborns with low birth weight as a result of infection with the plasmodium falciparum type. During pregnancy, the malaria parasite hides in the placental tissue. Parasite examination in pregnant women is done as a first step to detect and identify cases related to malaria control efforts.

This systematic study study and meta-analysis used research that controlled for confounding factors which could be seen from the study inclusion requirements, namely using multivariate analysis and the statistical result reported was the adjusted odd ratio (aOR). According to Murti (2018), confounding factor is the mixing of estimates of the relationship between exposure and the disease under study, by other factors related, both to disease and exposure. Confounding factors affect the relationship or effect of exposure to the disease occurrence estimated (estimated) by the study is not the same as the relationship or effect that actually occurs in the target population, or the study results are invalid (incorrect).

Estimates of the combined association of the effect of malaria infection with the incidence of LBW and preterm labor were processed using the RevMan 5.3 application with the generic inverse variance method. The results of the systematic review and meta-analysis of this study are presented in the form of a forest plot and a funnel plot.

The forest plot is a diagram that shows visually the amount of variation (heterogeneity), CI, the average between the study results examined in the meta-analysis. A funnel plot is a diagram in meta-analysis used to demonstrate possible publication bias. The funnel plot shows the relationship between the effect size of the study and the sample size of the various studies studied, which can be measured in a number of different ways (Murti, 2018).

The effect of malaria infection on the incidence of low birth weight

There are 13 observational research articles consisting of 4 cohort studies and 9 cross-sectional studies as a source of meta-analysis of the effect of malaria infection on the incidence of LBW. Analyzes were performed with subgroups of each observational study design. The results of the meta-analysis of the cohort study subgroup showed that malaria infection could increase the incidence of LBW by 1.31 times compared to the incidence of LBW that was not affected by malaria infection (aOR= 1.31; 95% CI= 0.90 - 1.90; p= 0.15). Meanwhile, the meta-analysis of cross-sectional studies showed that malaria infection could increase the incidence of LBW by 2.11 times compared to the incidence of LBW that was not affected by malaria infection (aOR 2.11; 95% CI 1.33 - 3.33; p = 0.001).

The results of this study are in line with the study conducted by Rudono et al. (2005) which stated that pregnant women infected with malaria in the first trimester have an increased risk of LBW by 5.9 times (aOR= 5.9; 95% CI= 1.02-34.11) higher than pregnant women who did not suffer from malaria during pregnancy. Pregnant women infected with malaria increased the incidence of LBW 6.2 times (aOR 6.2; 95% CI 1.83-32.85) higher than pregnant women who did not suffer from malaria in the second trimester. Pregnant women suffering from malaria due to plasmodium falciparum infection increased the incidence of LBW by 6.7 times higher than pregnant women who did not suffer from malaria (aOR 6.7; 95% CI 1.45-31.20).

Malaria can affect birth weight through anemia caused by plasmodium infection. Malaria can also reduce birth weight through the effects of placental infection. In this regard, parasites either directly cause mechanical impairment of placental circulation through extensive thickening of the trophoblast basement and increased fibrinoid necrosis and cyto-plasmic superiority or indirectly interfere with placental function and or cause pathological lesions. from 5 percent to 52 percent, the risk of LBW associated with infection increases two to four times in various studies (Uneke, 2007).

The results of a study conducted by Walther et al, (2010) in West Africa showed that babies born first to third to mothers with a history of malaria infection were significantly lighter, thinner, had lower BMI scores than babies of mothers without a history of malaria infection. Infants exposed to malaria infection were 2.4 times more likely to be thin at three months of age and 3.1 times more likely to be under-weight at 12 months of age than babies born to mothers without the infection

The results of research conducted by Omer et al. (2017) stated that placental malaria infection can increase the risk of maternal anemia and significantly affect the incidence of LBW by 25.2 times compared to pregnancies without placental malaria infection in pregnancy outcomes in the country of Sudan (aOR= 25.2; CI= 95% 15.1-41.3). This meta-analysis study con-cluded that malaria infection increases the risk of low birth weight.

AUTHOR CONTRIBUTION

Feri Yuda Anggara is the principal author who selects topics, explores and collects research data. Setyo Sri Rahardjo and Bhisma Murti played a role in analyzing the data and reviewing research documents

CONFLICT OF INTEREST

There is no conflict of interest in this study.

FUNDING AND SPONSORSHIP

This study uses funds from the Education Fund Management Institute (LPDP) of the Ministry of Finance of the Republic of Indonesia.

ACKNOWLEDGEMENT

We are very grateful to the database providers PubMed, ScienceDirect, Springer Link and Google Scholar.

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