

Unraveling Potential Confounding Variables in the Association Between Maternal Malaria and Child Stunting in Papua: A Case-Control Study with Mantel-Haenszel Analysis

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Abstract

Background: Papua is a malaria-endemic region with Indonesia's highest annual parasite incidence. At the same time, stunting is a common child health problem in Papua. Malaria incidence in pregnant women is considered a risk factor for stunting in children. Thus, the identification of confounding factors in this relationship is necessary.

Objective: The study aimed to determine significant confounding factors in maternal malaria and child stunting and clarify the true association between these two conditions.

Methods: The study with a case-control design was conducted at 14 Puskesmas from May to September 2023. The sample size was 681 children, consisting of toddlers who were stunted and not stunted and were selected by probability sampling technique. Data collection used questionnaires and anthropometric measurements. Statistical analysis used Mantel-Haenszel chi-square with a cut-off point for changes in the estimated coefficient for determining confounding > 10%.

Results: The results showed that the crude Odds Ratio of the effect of malaria incidence during pregnancy on the incidence of stunting in children was 1.746 (95% CI 1,062-2,872). Stratification analysis showed the adjusted Odds Ratio value of child sex (1.78), low birth weight (1.652), basic immunization status (1.771), breastfeeding status (1.753), maternal age (1.732), occupation (1.828), ethnicity (1.722) and family income (1.764). There were no potential confounding variables in the association between malaria incidence in pregnant women and childhood stunting (change in coefficient estimate <10%).

Conclusions: Public health interventions aimed at preventing malaria during pregnancy can be used as a strategy to reduce the risk of childhood stunting.

Keywords: Malaria; pregnancy; stunting; confounding; Indonesia

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Background

Malaria is one of the major health problems globally, especially in tropical and subtropical regions, with estimated global cases reaching millions each year (Varo, Chaccour, & Bassat, 2020). With its unique geographical and climatic conditions, the Papua region in Indonesia has one of the heaviest malaria burdens in the country (Hanandita & Tampubolon, 2016). In the past decade, despite intensive efforts in

malaria control, the incidence of malaria has continued to rise, especially among the most vulnerable populations, particularly pregnant women and young children (Park et al., 2020).

In parallel with malaria, child stunting is also a prominent health problem in Papua (Pemerintah Prov. Papua, 2022). Stunting, characterized by significantly shorter height than age standards, indicates chronic malnutrition and can predict various health and cognitive problems (Bhutta et al., 2017). It is estimated that more than 125 million pregnant women living in Plasmodium falciparum and P. vivax risk areas are at risk. Malaria contributes to a high burden of maternal morbidity and mortality in these areas and can affect placental development and fetal growth (Holger et al., 2016). Sequestration of P. falciparum-infected erythrocytes in the placenta is associated with maternal anemia, low birth weight, and an increased risk of infant mortality.

The impact of malaria on fetal growth is multifactorial, with factors such as maternal anemia, placental insufficiency, and inflammation playing a role (Holger et al., 2016). Currently, there is still uncertainty about the extent of the influence of malaria in pregnant women on the risk of child stunting. Previous research has shown that malaria during pregnancy is associated with an increased risk of preterm birth and low birth weight, both of which are risk factors for stunting (Holger et al., 2016). However, existing research often does not separate the effects of confounding factors that may contribute to the relationship between maternal malaria and child stunting, such as breastfeeding, dietary patterns, and socioeconomic factors.

Confounding is often referred to as "effect mixing," where the effect of the exposure under investigation is mixed with the effect of additional factors (or a set of factors) that distort the genuine relationship (Skelly, Dettori, & Brodt, 2012). According to Van Stralen, Dekker, Zoccali, and Jager (2010), specific criteria must be met to determine whether a variable can be considered a potential confounding variable. First, the variable must be associated with the exposure. Second, there must be a change in the estimated odds ratio (OR) coefficient with stratification of the potential confounding variable. Third, the variable should not mediate the exposure and outcome causal pathway. The second criterion is the primary guideline used in this research.

Studies related to the relationship between maternal malaria and child stunting have been conducted while considering several confounding variables. Amoah, Giorgi, Heyes, van Burren, and Diggle (2018) conducted research in Africa that controlled for economic status, gender, child's place of residence, and maternal education as confounding variables. In Brazil, research by Ferreira et al. (2015) controlled breastfeeding habits as a confounding variable. In West Africa, research on the relationship between malaria incidence and nutritional status considered ethnicity, economic status, body mass index, low birth weight, and maternal age to be controlled (Accrombessi et al., 2015). Research in Ethiopia examining the relationship between wasting and underweight incidence and malaria controlled for variables such as nutritional status, child gender, and maternal occupation (H. Hassen & Ali, 2015). Therefore, when analyzing the relationship between maternal malaria during pregnancy and child stunting in Papua, confounding analysis is necessary to ensure that maternal malaria is an independent risk factor for child stunting.

This study took a detailed and systematic approach to uncover potential confounding factors in the relationship between maternal malaria and child stunting in Papua. The research utilizes a case-control study design in 14 primary healthcare centers through probability sampling techniques and data collection involving questionnaires and anthropometric measurements. Identifying potential confounding variables can provide insights into the complex interaction between maternal malaria and child stunting. This information can be used to develop targeted interventions to prevent maternal malaria and child stunting. This study aims to determine significant confounding factors in maternal malaria and child stunting and clarify the true association between these two conditions.

Method

Study design and setting

This study employed a case-control design conducted in 14 Primary Health Centers (Puskesmas) in Papua, Indonesia, from May to September 2023. In 2022, the Annual Parasite Incidence (API) of malaria in Papua reached 113.07, significantly higher than the national API of Indonesia (1.61), with 4,239 reported cases of malaria in pregnant women. The prevalence of stunting among toddlers in Papua Province reached 34.6% in 2022, the third highest nationally. This represents a 5.1 percentage point increase from the previous year (2021: 29.5%).

Sample

The sample size for the study was calculated using the formula by Lemeshow, Jr, Klar, and Lwanga (1990) with a 95% confidence interval, 80% power (0.84), OR = 1.9 (Gari, Loha, Deressa, Solomon, & Lindtjørn, 2018), and a case-to-control ratio of 1:2. The total sample size for this study was 681 children (Cases: 227 and Controls: 454), consisting of toddlers with stunting and those with average growth. Inclusion criteria for cases were toddlers diagnosed with stunting based on the World Health Organization (WHO) growth parameters, while the control group consisted of toddlers with average growth. Sample selection was conducted using probability sampling techniques to ensure that each individual had an equal chance of being selected.

Inclusion and exclusion criteria were established for both subject groups. In the case group, inclusion criteria comprised toddlers aged 0-59 months diagnosed with stunting, defined as having a z-score of less than -2.00 SD (stunted) and less than -3.00 SD (severely stunted), possessing complete anthropometric data (height, weight), and having a mother with a documented history of pregnancy and childbirth within the study area. Conversely, for the control group, inclusion criteria encompassed toddlers of the same age range who were not diagnosed with stunting and resided in the same geographical area. Exclusion criteria for both groups included toddlers with specific growth disorders, a history of severe illnesses affecting growth, and incomplete data regarding anthropometric status or maternal pregnancy history.

Instrument and data collection

Data were collected through questionnaires filled out by the parents or guardians of the children and anthropometric measurements of the children. The questionnaire was designed to gather information on maternal malaria during pregnancy, child sex, birth weight, basic immunization status, breastfeeding status, maternal age, occupation, ethnicity, and family income. The determination of stunting status was based on records from the Primary Health Centers recorded in the Community-Based Nutrition Recording and Reporting System (e-PPGBM). Using standardized and calibrated equipment, including height, weight, and other relevant parameters, trained healthcare personnel carried out anthropometric measurements.

Data collection was conducted during Posyandu activities. Home visits if the selected child sample did not attend the Posyandu. Data collection was assisted by enumerators who were nutrition officers from the Puskesmas. Before data collection, researchers explained each questionnaire item and how to fill it out. To ensure the quality of research data, quality control of data collection was carried out by filling out questionnaires using the interview method (the questionnaire filler is the enumerator) and rechecking the filled questionnaires. The enumerator also performs verification and clarification if there are discrepancies between the interview data and the data from the Community-Based Nutrition Recording and Reporting System (e-PPGBM).

Data analysis

Statistical analysis was conducted by stratification using the Mantel-Haenszel chi-square test to assess the relationship between maternal malaria and child stunting while considering potential confounding variables (Pourhoseingholi, Baghestani, & Vahedi, 2012). Initial data analysis included a test to determine the effect of malaria during pregnancy on the occurrence of stunting to obtain the Crude Odds Ratio (OR) with a 95% Confidence Interval. Subsequently, stratification was performed by including potential confounding variables (child sex, birth weight, basic immunization status, breastfeeding status, maternal age, occupation, ethnicity, and family income) to obtain Adjusted Odds Ratio (OR) values. The change in coefficient estimation was calculated using the coefficient change formula (Figure 1) (Talbot, Diop, Lavigne-Robichaud, & Brisson, 2021). The cut-off point for coefficient change to be considered as confounding was set at >10%, as used in previous studies (Budtz-Jørgensen, Keiding, Grandjean, & Weihe, 2007; Hourlier, Reina, & Fennema, 2015; Howards, 2018). The Mantel-Haenszel test was conducted using SPSS version 20.

We also conducted analyses of the Test of Conditional Independence and the Test of Homogeneity of the Odds Ratio (Breslow-Day). The Test of Conditional Independence aims to assess whether there is a significant relationship between two categorical variables (malaria during pregnancy and the occurrence of stunting) after controlling or adjusting for stratification by categorical confounding variables ($p < 0.05$) (Adetunji, Jemilohun, & Adaraniwon, 2015; Zhang & Tinker, 2019). The Test of Homogeneity of the Odds Ratio (Breslow-Day) is used to evaluate whether the estimated association between malaria during pregnancy and the occurrence of stunting is the same in all strata or subgroups identified in the Mantel-Haenszel analysis (homogeneity $p > 0.05$) (Adetunji et al., 2015; Zhang & Tinker, 2019).

Ethical consideration

This study was approved by the Health Research Ethics Committee Health Polytechnic of Jayapura (reference number 109/KEPK-J/V/2023) and performed following the principles of the Declaration of Helsinki. All respondents who agreed to participate as samples declared their willingness by signing the informed consent form.

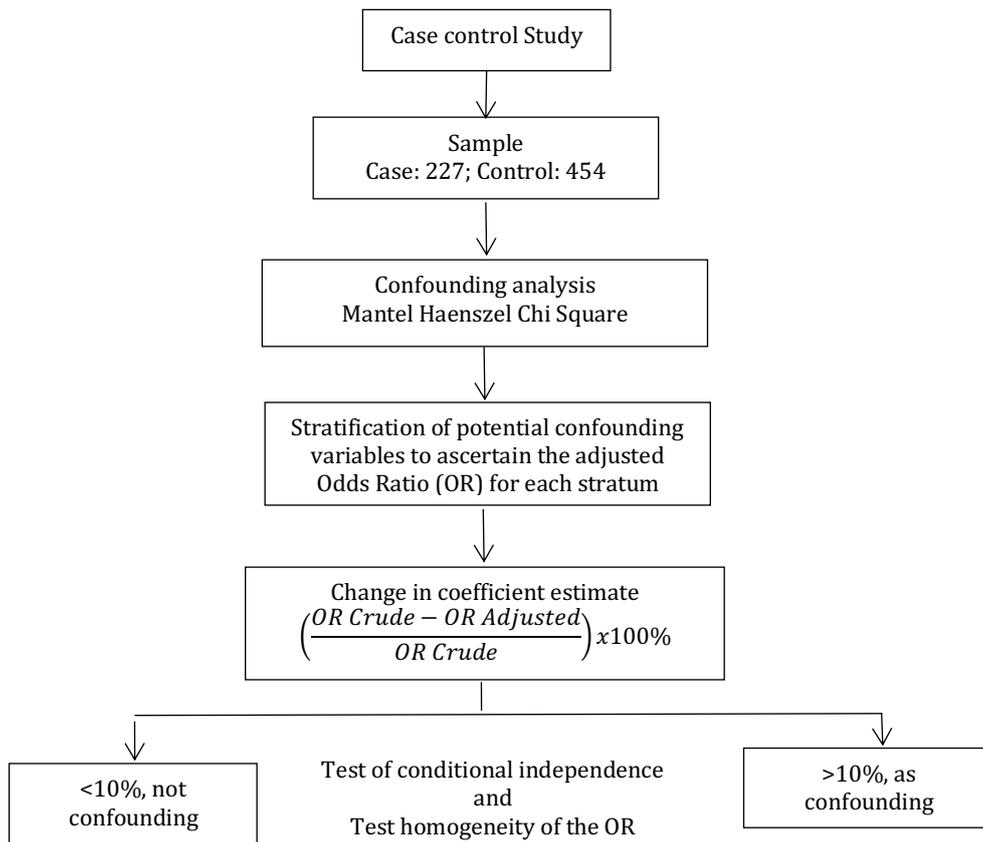


Figure 1. Stratification Mantel - Haenszell chi square analysis

Result

Table 1 shows that the prevalence of child stunting among female children whose mothers experienced malaria during pregnancy is 17.3%. Female children whose mothers had malaria during pregnancy are more likely to experience stunting compared to those whose mothers did not have malaria during pregnancy (OR = 2.036, 95% CI 1.040 - 3.984). The prevalence of child stunting among those who did not receive Exclusive Breastfeeding from mothers with malaria during pregnancy is 14.3%. Children who did not receive Exclusive Breastfeeding from mothers with malaria during pregnancy have a higher likelihood of experiencing stunting (OR = 2.096, 95% CI 1.069 - 4.113). About 13.2% of stunting cases occurred in children whose mothers were not employed and had malaria. Children whose mothers were not employed and had malaria are 1.937 times more likely (95% CI 1.097 - 3.422) to stunting compared to those without malaria.

Table 1 Stratification of the Relationship Between Malaria During Pregnancy and the Incidence of Stunting Based on Demographic and Socioeconomic Variables

Characteristic variables	Malaria during pregnancy	Stunting				p-value stratum	OR Stratum (CI 95%)
		Stunted (n=227)		Not stunted (n=454)			
		n	%	n	%		
Child sex							
Man	Yes	14	11.4	17	7.8	0.363	1.519 (0.721-3.198)
	No	109	88.6	201	92.2		
Female	Yes	18	17.3	22	9.3	0.054*	2.036 (1.040 - 3.984)
	No	86	82.7	214	90.7		
Birth weight							
LBW	Yes	9	30.0	5	14.3	0.217	2.571 (0.754 - 8.773)
	No	21	70.0	30	85.7		
Not LBW	Yes	23	11.7	34	8.1	0.203	1.497 (0.856 - 2.617)
	No	174	88.3	385	91.9		
Basic immunization status							
Not Complete	Yes	6	14.6	3	5.0	0.189	3.257 (0.765 - 13.863)
	No	35	85.4	57	95.0		
Complete	Yes	26	14.0	36	9.1	0.106	1.616 (0.944 - 2.767)
	No	160	86.0	358	90.9		
Breastfeeding status							
Not Exclusive	Yes	19	14.3	19	7.4	0.045*	2.096 (1.069 - 4.113)
	No	114	85.7	239	92.6		
Exclusive	Yes	13	13.8	20	10.2	0.476	1.412 (0.670 - 2.979)
	No	81	86.2	176	89.8		
Maternal age							
At risk	Yes	5	11.4	8	11.6	1.000	0.978 (0.298 - 3.205)
	No	39	88.6	61	88.4		
Not at risk	Yes	27	14.8	31	8.1	0.021*	1.976 (1.141 - 3.423)
	No	156	85.2	354	91.9		
Occupation							
Working	Yes	6	20.0	12	14.5	0.675	1.479 (0.500 - 4.372)
	No	24	80.0	71	85.5		
Not working	Yes	26	13.2	27	7.3	0.031*	1.937 (1.097 - 3.422)
	No	171	86.8	344	92.7		
Ethnicity							
Papua	Yes	20	14.4	22	9.3	0.183	1.635 (0.857 - 3.118)
	No	119	85.6	214	90.7		
Non Papua	Yes	12	13.6	17	7.8	0.173	1.867 (0.852 - 4.092)
	No	76	7.8	201	92.2		
Family income							
< minimum wage	Yes	28	13.9	31	8.4	0.053*	1.770 (1.029 - 3.046)
	No	173	86.1	339	91.6		
≥ minimum wage	Yes	4	15.4	8	9.5	0.633	1.727 (0.475 - 6.279)
	No	22	84.6	76	90.5		

The research results also indicated an incidence rate of child stunting in families with income < City of Jayapura's Minimum Wage (UMR) whose mothers had malaria during pregnancy at 13.9%, with an OR 1.770 (1.029 - 3.046). About 14.8% of stunting cases occurred in children whose mothers were categorized as not at risk in terms of age and had malaria. Children whose mothers were classified as not at risk in terms of age and had malaria are 1.976 (95% CI 1.141 - 3.423) times more likely to experience stunting compared to those without malaria. **Table 1** also shows that based on the stratified analysis, there is no difference in the risk of stunting for the variables of birth weight, basic immunization status, and ethnicity for mothers with malaria and those without malaria ($p > 0.05$).

Table 2 Mantel-Haenszel Chi-Square Test

Characteristic variables	Test of conditional independence		Test homogeneity OR Breslow-Day (p-value)	OR Crude (CI 95%)	OR adjusted (CI 95%)
	Nilai p Cochrane	p value Mantel-Haenszel			
Child sex	0.022	0.031	0.566	1.746 (1.062-2.872)	1.780 (1.082-2.931)
Birth weight	0.051	0.029	0.430	1.746 (1.062-2.872)	1.652 (0.997 – 2.735)
Basic immunization	0.024	0.034	0.369	1.746 (1.062-2.872)	1.771 (1.074 – 2.921)
Breastfeeding status	0.026	0.036	0.441	1.746 (1,062-2,872)	1.753 (1.065 – 2.884)
Maternal age	0.028	0.039	0.288	1.746 (1.062-2.872)	1.732 (1.054 – 2.845)
Occupation	0.017	0.025	0.665	1.746 (1.062-2.872)	1.828 (1.106 – 3.021)
Ethnicity	0.031	0.043	0.798	1.746 (1.062-2.872)	1.722 (1.046 – 2.837)
Family income	0.025	0.035	0.973	1.746 (1.062-2.872)	1.764 (1.069 – 2.909)

Table 2 showed that based on the Test of Conditional Independence Mantel-Haenszel, the significant p-values (<0.05) indicate that the relationship between maternal malaria during pregnancy and stunting remains significant even after controlling for other variables for male children (p=0.031), incomplete basic immunization status (p=0.034), non-exclusive breastfeeding (p=0.036), mothers at risk in terms of age (p=0.039), working mothers (p=0.025), Papua ethnicity (p=0.043), and family income below the minimum wage (p=0.035). This confirms that malaria during pregnancy is an independent risk factor for the occurrence of child stunting.

Table 2 also presented the results of the Test of Homogeneity of the Odds Ratio (Breslow-Day) with p-values, indicating that there is homogeneity in the effect of maternal malaria on the risk of stunting in all analyzed subgroups (child sex, birth weight, basic immunization status, breastfeeding status, maternal age, occupation, ethnicity, and family income) with p-values >0.05. This suggests that the effect of malaria on the risk of stunting does not significantly differ among various strata of the analyzed variables.

Table 3 Coefficient Estimation Change

Characteristic variables	OR Crude	OR Adjusted	Changes in the estimated coefficient (%)	Status
Child sex	1.746	1.780	1.95	Not confounding
Birth weight	1.746	1.652	5.38	Not confounding
Basic immunization status	1.746	1.771	1.43	Not confounding
Breastfeeding status	1.746	1.753	0.40	Not confounding
Maternal age	1.746	1.732	0.80	Not confounding
Occupation	1.746	1.828	4.70	Not confounding
Ethnicity	1.746	1.722	1.37	Not confounding
Family income	1.746	1.764	1.03	Not confounding

Table 3 indicates that although there were changes in the adjusted OR values for all characteristic variables, the change in coefficients for all variables was less than 10%. This suggests that child sex, birth weight, basic immunization status, breastfeeding status, maternal age, occupation, ethnicity, and family income are not confounding variables in the relationship between maternal malaria during pregnancy and the occurrence of child stunting.

Discussion

The research findings indicate that female children whose mothers experienced malaria during pregnancy have a stunting prevalence of 17.3%, with a higher risk of stunting (OR=2.036) compared to those whose mothers did not experience malaria. A longitudinal study conducted in Ethiopia, India, Peru, and Vietnam found that child characteristics such as age, sex, and birth weight have been identified as determinants of stunting (Wake, Zewotir, Lulu, & Fissuh, 2023). A similar pattern is observed in children who did not receive exclusive breastfeeding from mothers with malaria during pregnancy, with a higher risk of stunting (OR=2.096). Exclusive breastfeeding, in particular, has been associated with a lower risk of stunting (Hadi & Fatimatasari, 2021). Breast milk provides essential nutrients and growth factors crucial for a child's growth and development. Breastfeeding also helps protect against infections, which can contribute to stunting (Campos, Vilar-Compte, & Hawkins, 2020).

Stunting is also associated with socioeconomic factors such as family income. For instance, children from families with incomes below the City of Jayapura's Minimum Regional Wage (UMR) have an OR of 1.770 for stunting if their mothers had malaria during pregnancy. Stunting is more common in children from lower-income households than those from higher-income ones. Stunting can result from poverty, leading to insufficient food intake, reduced food access, and limited access to sanitation, clean water, and healthcare (Azmeraw, Akalu, Boke, & Gelaye, 2021). According to research by Gone, Lemango, Eliso, Yohannes, and Yohannes (2017), children's nutritional status is significantly influenced by Plasmodium exposure. Additionally, sociodemographic variables like family income can affect whether children experience malnutrition and can increase the risk of morbidity in children living in malaria-endemic areas due to malnutrition.

The result of the crude odds ratio of the effect of malaria incidence during pregnancy on the incidence of stunting in children was 1.746 (95% CI 1.062-2.872). Previous research has highlighted how placental malaria can lead to intrauterine hypoxia and maternal anemia, both known to affect fetal growth negatively (Holger et al., 2016). Furthermore, our stratification analysis results indicate that malaria during pregnancy is an independent risk factor for stunting, not significantly influenced by other confounding variables such as birth weight and immunization status. Randomization or statistical analysis ensures the relationship between risk factors and outcomes due to the risk factor and not confounding variables (Bendabenda et al., 2018). Several studies also confirm that gender and ethnicity are not confounding variables in the relationship between malaria incidence and malnutrition (H. Y. Hassen & Ali, 2016; Mann, Swahn, & McCool, 2021; Wilson et al., 2018).

Testing the homogeneity of effects using the Breslow-Day Test indicates that the effect of malaria on stunting is consistent across all subgroups we analyzed. These results confirm that malaria during pregnancy has a specific detrimental effect on the risk of stunting, regardless of other factors typically associated with child growth. In research conducted in West Africa, statistical control of birth weight was performed, and the results showed that malaria incidence impacts infant hemoglobin levels (Accrombessi et al., 2015). Different results were found in a study conducted in Uganda by De Beaudrap et al. (2016), which found that malaria infection during pregnancy was associated with a higher risk of stunting at six months of age. Still, this association was no longer significant after controlling for confounding factors such as birth weight, breastfeeding, and socioeconomic status.

The findings of this research reinforce the need for comprehensive health policies and interventions designed to prevent malaria during pregnancy as part of a broader strategy to address stunting. Preventing malaria during pregnancy should not only be considered a crucial step in directly protecting the health of both mother and child but also a critical component in reducing the prevalence of stunting and improving long-term health outcomes for children (Schantz-Dunn & Nour, 2009). Interventions such as insecticide-treated bed nets, intermittent preventive treatment during pregnancy, and improved access to quality prenatal care can be focal points for reducing the burden of malaria and stunting simultaneously (Al Khaja & Sequeira, 2021; Desai et al., 2018).

In this study, significant limitations are present in terms of design and methodological constraints, as well as potential confounding factors that have not been considered. As a case-control study, it inherently is unable to establish causality; the findings can only suggest associations and cannot definitively prove that maternal malaria leads to child stunting. Additionally, while the study accounts for several potential confounders, such as child sex, birth weight, and maternal age, other unmeasured variables could influence the results, including dietary patterns, genetic factors, or other environmental exposures, which were not explored in this research. This omission could affect the validity and applicability of the study's conclusions.

Conclusion

There were no potential confounding variables in the association between malaria incidence in pregnant women and childhood stunting. Public health interventions aimed at preventing malaria during pregnancy can be used as a strategy to reduce the risk of childhood stunting. Longitudinal studies can be conducted to track the long-term health outcomes of children born to mothers who experienced malaria during pregnancy, providing valuable insights into the persistence of stunting and its broader implications on child development.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Author Contributions

ZRF and MS contributed to the preparation of the study design, literature search, data collection, preparation of reports, Writing-original draft and manuscript publication.

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