nature portfolio

Peer Review File

Evidence and Opportunities for Preeclampsia and Cardiovascular Disease in Malaria Endemic Settings

Corresponding Author: Dr Zainab Mahmoud

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This manuscript is a Perspective. The authors are providing us with a challenge: to consider the role of preventing malaria in pregnancy (in particular, placental malaria) as a means to reduce the risk of preeclampsia and maternal cardiovascular disease in malaria-endemic settings. The observation that malaria in pregnancy and preeclampsia share pathways and outcomes is not a novel concept (as the authors have also noted in their review of the literature); however, what the authors propose is using malaria prevention strategies as tools to reduce the burden of preeclampsia and cardiovascular disease. This deserves more attention and a call to design and execute appropriate trials to test the several hypotheses that need to be formulated.

In general, the manuscript is well written and makes strong points that will generate discussion (permitted by the narrower scope of a Perspective article compared to a Review article).

I have a couple of minor comments:
1. The authors state"(...) impaired trophoblast invasion and incomplete spiral artery remodeling are observed in both conditions, resulting in reduced placental perfusion and placental insufficiency" and cite a review. I wonder how confident we can be that this is actually the case for malaria in pregnancy. I personally agree with the authors, but would be careful to state it in such a definitive fashion.

2. What do the authors believe is the role of existing biomarkers of preeclampsia in monitoring this condition in malaria-endemic settings, alongside mRDTs? I'm thinking of the sFlt1/PlGF ratio, for example (https://www.nejm.org/doi/full/10.1056/NEJMoa1414838)

3. What can we learn from the different malaria treatment regimens during pregnancy and how they modify the association between malaria and preeclampsia? IPTp-SP, for example, seems to improve pregnancy outcomes even in the absence of an effect on malaria in pregnancy. Does it impact preeclampsia? (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(25)00405-X/fulltext). Could a mechanistic link be inferred from the data generated from trials comparing different IPTp regimens?

4. Given the possibility that defects in placentation could be directly related to the link between malaria and preeclampsia, could the authors comment on the feasibility of including pre-pregnancy malaria treatment (pre-placentation) as an effective tool to add to the discussion?

5. Can the authors provide an insight into how challenging it would be to operationalise the monitoring of these two (three) conditions in malaria-endemic areas?

I look forward to seeing the discussion and work spurred by this manuscript.

Reviewer #2

(Remarks to the Author)

In this review article the authors summarized some of the literature describing placental malaria (PM) and preexclampsia (PE) and attempted to provide a future plan.
Comments
1. Abstract: “Plasmodium falciparum infection, the dominant cause of placental malaria in sub-Saharan Africa may increase preeclampsia risk” the way written suggest casual pathway while studies suggest an association.
2. Background: no references provide for the following statement “placental pathophysiology including vascular dysfunction, inflammation, oxidative damage and impaired perfusion with significant contribution to maternal and perinatal morbidity and mortality”.
3. The authors should specify which observations were derived from animal models and which from human studies. For example: “This sequestration promotes accumulation of monocytes and macrophages and elevated tumor necrosis factor-α (TNF-α), contributing to chronic placental inflammation and dysfunction”
4. “Physical disruption of syncytiotrophoblast is another shared characteristic, with breakages of the syncytium and oxidative damage contributing to cellular damage and dysfunction”. These are some features of placental malaria but rates vary, can you add rates or most frequent to least frequent feature for each of the syndromes (PE and PM).
5. “Both placental malaria and preeclampsia are associated with reduced nitric oxide bioavailability, endothelial activation, and loss of vascular integrity, leading to widespread vascular dysfunction and impaired uteroplacental blood flow.” Can you provide some data to support the associations between PM and these changes instead of another review article.
6. “Additionally, impaired trophoblast invasion and incomplete spiral artery remodeling are observed in both conditions” Please provide a reference for a study that showed incomplete spiral artery remodeling associated with PM.
7. “These pathological changes lead to similar adverse pregnancy outcomes, such as intrauterine growth restriction” Lead or associated with?
8. “A Research and Implementation Agenda for Malaria-Aware Preeclampsia Prevention” It is not clear what new alternative or approaches the authors proposed.
The first item epidemiological studies, there might be data already collected in some small studies, like the study by Obiri et al in which unfortunately the model wasn’t adjusted for SP. But the main issue at hand is that the benefit of IPTp-SP has been described and is well known in preventing PM. Also, the failure in successful implementation of IPTp have been described, here the authors did not propose anything new. ANC visits are supposed to include BP exam and malaria chemoprevention, how the integrated approach the authors refer to is different? how will that be implemented any better?

Reviewer #3

(Remarks to the Author)
Thank you for the invitation to review this short communication. It is a useful review however it requires a few updates of recent evidence before it is published.

The title
1.While pre-eclampsia and eclampsia are associated with worse pregnancy outcomes than gestational hypertension it may be work considering hypertensive disorders of pregnancy rather than ‘pre-eclampsia’ alone in the title. It is not just preeclampsia that is associated with later onset chronic hypertension and cardiovascular risk. This applies to the manuscript as a whole.

Background
2.As the manuscript title includes “evidence” i.e. Malaria, Preeclampsia, and Cardiovascular Disease: Evidence and Opportunities; it should therefore give credit to Wickramamasuriya G.A.W., who provided the first descriptions of the link between Pre-eclampsia, Eclampsia and Malaria during his work during malaria epidemics in tea plantations in Ceylon (now Sri-Lanka) (cite Wickramamasuriya G.A.W., Malaria and Ankylostomiasis in the Pregnant Woman, Oxford University Press 1937. London, UK) nearly a century ago.

3.In this sentence: “Malaria in pregnancy remains a major driver of maternal anemia, low birthweight, fetal and neonatal death across much of Africa.” Yet reference 6 (systematic review and meta-analysis) includes SGA and Preterm birth which are significantly more informative than LBW, of the harmful impact of malaria. Suggestion to drop LBW and include SGA and PTB.

4.Consider adding the problem of intergenerational effects of malaria and of hypertensive disorders of pregnancy (HDoP) as another reason to prevent them. References could include for malaria (Saito M, et al. Deleterious effects of malaria in pregnancy on the developing fetus: a review on prevention and treatment with antimalarial drugs. The Lancet Child & Adolescent Health, 4, 761-774) and for HDoP, Xiong J, et al. Intergenerational Associations of Hypertensive Disorders of Pregnancy With Offspring Metabolomics: A Systematic Review. Matern Fetal Med. 2025 Jul;7(3):157-165. doi: 10.1097/FM9.0000000000000276. Epub 2025 Mar 17. PMID: 41608203

Evidence Linking Falciparum Malaria and Preeclampsia (reconsider hypertensive disorders of pregnancy)
5.The explanation of reference 10 from SE Asia is not completely correctly presented. True and important to retain: all women were followed from 1st trimester, and the associations were strongest at 14 weeks gestation compared with 28 weeks. Not all women in the SE cohort had falciparum malaria but all women were screened for falciparum and vivax malaria on multiple occasions. Among primigravidae, falciparum malaria was associated with pre-eclampsia/eclampsia (AOR 2.61, 95%CI 1.01–6.79) while among multigravidae, falciparum malaria was associated with gestational hypertension (adjusted odds ratio (AOR) 2.59, 95%CI 1.59–4.23), compared to women with no malaria. And as the argument in this Communications manuscript is on the dangers of falciparum and PE you might consider adding that in the same cohort there

was no increased risk conferred by vivax malaria, to highlight falciparum.

6.Variability of the associations reported to date including in Syst Revs and Metas needs a comment: e.g. ref 6 insignificant assoc with pre-ec, ref 8 risk of pre-ec in MG, ref 9 only 4 studies included and all types of HTN pooled, ref 10 both GH and pre-ec/ec different risk in PG and MG. The quality of the data is important.

7a.Rethink/update the statements on malaria prevention: SP is an antifolate and cannot be given in trimester one when formation of the placenta commences. Indeed, the average gestation of first dose of SP is largely timed, in practice, with the end of placenta formation i.e around 20 weeks (although the WHO recommendations are for earlier uptake i.e. 13 weeks). Hence it will never be administered in a timely way to impact formation of the placental vasculature. 30 years of trying to improve the early and consistent uptake of SP has not had the impact hoped, not to mention areas where SP is not effective due to drug resistance. The same problems are likely to haunt any role out Aspirin.

7b. Please modify statements on Calcium given new evidence that suggests the purported benefits may be far less significant — and potentially absent —it may not work at all: Cluver CA, Rohwer C, Rohwer AC. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews 2025, Issue 12. Art. No.: CD001059. DOI: 10.1002/14651858.CD001059.pub6. Accessed 28 March 2026.

7c. At least Aspirin could start with SP but unfortunately evidence of daily medications adherence in pregnant women is also needed.

7d. Given the problems i.e. the gestation of implementation (SP, Aspirin) occur after/or too late to completely prevent adverse placentation please consider alternative prevention/s. Pre-conception malaria prevention with long acting antimalarials (ACT with long acting partner) or potentially vaccines (administered with presumptive treatment) to women of child bearing age will be needed to break the linkage of deleterious affects on placentation. See the recently reported trial: Diawara H, et al. Safety and efficacy of PfSPZ Vaccine against malaria in healthy adults and women anticipating pregnancy in Mali: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis. 2024 Dec;24(12):1366-1382. doi: 10.1016/S1473-3099(24)00360-8. Epub 2024 Aug 14. PMID: 39153490; PMCID: PMC12117479.

7e. Inevitably, these type of trials (as above) are/will be an excellent source of data for risk of Hypertensive disorders of pregnancy? As long as standardised efforts to record hypertension and test sticks for protein AND linkage between antenatal care records and birth centres are complete.
7f. Advocate for preconception studies (Yanow S, Vinals D Preconception immunisation to prevent pregnancy-associated malaria. The Lancet Infectious Diseases, 2024; 24, 1296-1298

8.Missing evidence
While the authors outline the requirement for good definitions and diagnostics for malaria and hypertensive disorders of pregnancy the role of nutrition cannot be ignored. In future prospective trials need to account for the rapid changes in the double burden of malnutrition in LMIC and its links to epigenetics (Hoffman DJ, et al., Developmental origins of metabolic diseases. Physiol Rev. 2021 Jul 1;101(3):739-795. doi: 10.1152/physrev.00002.2020. Epub 2020 Dec 3. PMID: 33270534) by recording the most basic of data in pregnancy i.e. at a minimum height and weight so that BMI and GWG can be accounted for. Ideally a measure of gestational diabetes is also needed.

9. Suggest to recommend/reference free standardised resources e.g. https://intergrowth21.com/course/evidence-based-management-pre-eclampsia-and-eclampsia-interactive-course-health

Conclusion
10. "…building antenatal care models that integrate malaria control and cardiovascular risk reduction, and ensuring that guidelines and policies in endemic regions reflect these needs…" Is not enough. Why? For women in low resource setting the event of the terminal outcomes of pregnancy including: severe gestational hypertension, pre-eclampsia or eclampsia requiring induction, urgent or operative delivery; does not get linked to antenatal events (timing and uptake of SP, use of pre-eclampsia prevention) as it can take place in a completely different part of the health system i.e. hospital rather than clinic.

11. 2nd sentence "…However, in high malaria-transmission regions…", reference 10 is not high transmission. Wherever women have a risk of falciparum in early pregnancy there is a risk of HDoP. Suggest caution throughout the manuscript in relation to level of transmission. One might imagine it would be easier to measure outcomes in high transmission areas as data can be accumulated more quickly than in a low transmission settings if there is an effective intervention, but maybe not as immunity, may be a contributing factor i.e. the difference in HDoP by parity.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This is a revised Perspectives article in which the authors argue for malaria prevention as a means of reducing pre-eclampsia and, subsequently, the risk of cardiovascular disease later in life. As a Perspectives article, the authors have

more room to speculate and put their opinions forward.

The authors have improved the manuscript and addressed my comments. I have only minor comments that the authors could address prior to publication, at the discretion of the editors:

1- There is some inconsistency in the nomenclature of Plasmodium falciparum. The authors could standardise it.

2- In the main text of the article (excluding the abstract), the authors introduce placental malaria as a new term in line 96. It is a bit jarring since there has been, up to this point, no mention that malaria in pregnancy can result in placental malaria. Maybe a connecting sentence before this would suffice.

3- Line 152 could cut the words " with antimalarials".

4- The order in which arguments are presented in the "Malaria Prevention as Cardiovascular Disease Prevention" section could be changed to bring the association between preeclampsia and cardiovascular disease forward to establish a framework that justifies the remaining points in that section.

Reviewer #2

(Remarks to the Author)
The authors responded to the comments and I don't have any additional comments.

Reviewer #3

(Remarks to the Author)
I am satisfied with the authors rebuttal and the improved manuscript. Well done.

Response to Editors and Reviewers

Revised Manuscript Title: Evidence and Opportunities for Preeclampsia and Cardiovascular Disease in Malaria Endemic Regions

We thank the editors and reviewers for their thoughtful, insightful, and constructive feedback on our manuscript. We are grateful for the time and effort dedicated to the review process and for the opportunity to revise our work. We have carefully reviewed each comment and revised the manuscript to address all concerns. Below is a detailed, point-by-point response outlining our changes clarifications. We have also included a revised manuscript with changes tracked.

Reviewers' comments:

Reviewer #1:

This manuscript is a Perspective. The authors are providing us with a challenge: to consider the role of preventing malaria in pregnancy (in particular, placental malaria) as a means to reduce the risk of preeclampsia and maternal cardiovascular disease in malaria-endemic settings. The observation that malaria in pregnancy and preeclampsia share pathways and outcomes is not a novel concept (as the authors have also noted in their review of the literature); however, what the authors propose is using malaria prevention strategies as tools to reduce the burden of preeclampsia and cardiovascular disease. This deserves more attention and a call to design and execute appropriate trials to test the several hypotheses that need to be formulated. In general, the manuscript is well written and makes strong points that will generate discussion (permitted by the narrower scope of a Perspective article compared to a Review article).

I have a couple of minor comments:

1) *The authors state"(...) impaired trophoblast invasion and incomplete spiral artery remodeling are observed in both conditions, resulting in reduced placental perfusion and placental insufficiency" and cite a review. I wonder how confident we can be that this is actually the case for malaria in pregnancy. I personally agree with the authors, but would be careful to state it in such a definitive fashion.*

We agree with the concerns raised and have revised the sentence to state that: impaired trophoblast invasion and incomplete spiral artery remodeling are well-established features of preeclampsia and have also been suggested in malaria in pregnancy, potentially contributing to reduced placental perfusion and insufficiency. We have also included additional citation to support the statement.

Changes to manuscript: Lines 129-131

2) *What do the authors believe is the role of existing biomarkers of preeclampsia in monitoring this condition in malaria-endemic settings, alongside mRDTs? I'm thinking of the sFlt1/PlGF ratio, for example (https://www.nejm.org/doi/full/10.1056/NEJMoa1414838)*

We thank the reviewer and have added a brief note on the potential role of the sFlt-1/PlGF ratio alongside malaria diagnostics, while acknowledging current evidence gaps.

Changes to manuscript: Lines 237-245

3) *What can we learn from the different malaria treatment regimens during pregnancy and how they modify the association between malaria and preeclampsia? IPTp-SP, for example, seems to improve pregnancy outcomes even in the absence of an effect on malaria in pregnancy. Does it impact preeclampsia? (https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(25)00405-X/fulltext). Could a mechanistic link be inferred from the data generated from trials comparing different IPTp regimens?*

Noted with thanks. We have added a brief note in the manuscript stating that IPTp-SP has been associated with improved birth outcomes even when malaria reductions is limited, suggesting effects beyond parasite clearance. Whether this extends to preeclampsia is unknown. Comparative IPTp trials may help evaluate causal links between malaria, placental dysfunction, and preeclampsia; however, blood pressure and other vascular outcomes remain underexplored in the existing literature.

Changes to manuscript: Lines 178-190

4) *Given the possibility that defects in placentation could be directly related to the link between malaria and preeclampsia, could the authors comment on the feasibility of including pre-pregnancy malaria treatment (pre-placentation) as an effective tool to add to the discussion?*

As suggested, we have included a text to address this: As early placentation represents a critical window, pre-pregnancy malaria prevention may offer an additional preventive strategy, but its impact on placentation and preeclampsia risk is unknown.

Changes to manuscript: Lines 178-190

5) *Can the authors provide an insight into how challenging it would be to operationalise the monitoring of these two (three) conditions in malaria-endemic areas?*

Thank you, we have added a brief discussion on the feasibility of integrated monitoring, noting both existing constraints and the opportunity to leverage antenatal care programs for implementation.

Changes to manuscript: Lines 214-221

I look forward to seeing the discussion and work spurred by this manuscript.

Thank you.

Reviewer #2:

In this review article the authors summarized some of the literature describing placental malaria (PM) and preexclampsia (PE) and attempted to provide a future plan.

1) *Abstract: "Plasmodium falciparum infection, the dominant cause of placental malaria in sub-Saharan Africa may increase preeclampsia risk" the way written suggest casual pathway while studies suggest an association.*

This has been revised to state: Increasing evidence suggests that infection with Plasmodium falciparum, which causes placental malaria, is associated with increased preeclampsia risk. Here we discuss how epidemiologic and biological evidence link malaria to preeclampsia by examining shared pathways, including placental inflammation and vascular disruptions, that culminate in the unifying phenomenon of placental dysfunction in both syndromes. With these shared mechanisms in mind, we discuss how malaria prevention strategies could reduce the risk of preeclampsia and related long-term cardiovascular disease in endemic settings.
Changes to manuscript: Lines 53-55

2) *Background: no references provide for the following statement "placental pathophysiology including vascular dysfunction, inflammation, oxidative damage and impaired perfusion with significant contribution to maternal and perinatal morbidity and mortality".*

Appropriate citations have been included

Changes to manuscript: Line 78

3) *The authors should specify which observations were derived from animal models and which from human studies. For example: "This sequestration promotes accumulation of monocytes and macrophages and elevated tumor necrosis factor-α (TNF-α), contributing to chronic placental inflammation and dysfunction"*

We have revised the statement to state: This sequestration promotes accumulation of monocytes and macrophages and elevated tumor necrosis factor-α (TNF-α), contributing to chronic placental inflammation and dysfunction, as observed in human placental studies and supported by experimental models

Changes to manuscript: Line 119-122

4) *"Physical disruption of syncytiotrophoblast is another shared characteristic, with breakages of the syncytium and oxidative damage contributing to cellular damage and dysfunction". These are some features of placental malaria but rates vary, can you add rates or most frequent to least frequent feature for each of the syndromes (PE and PM).*

We thank the reviewer for this comment. While several studies describe syncytiotrophoblast disruption and oxidative stress in both preeclampsia and placental malaria, the cited literature does not provide standardized or comparable prevalence estimates across conditions. We have revised the text to clarify that these features are reported in both conditions, while noting that their prevalence varies widely across studies and is not directly comparable.

Changes to manuscript: Lines 127-131

5) *"Both placental malaria and preeclampsia are associated with reduced nitric oxide bioavailability, endothelial activation, and loss of vascular integrity, leading to widespread*

vascular dysfunction and impaired uteroplacental blood flow." Can you provide some data to support the associations between PM and these changes instead of another review article.

As suggested, we have added quantitative evidence from human studies demonstrating reduced nitric oxide bioavailability in placental malaria, including significantly higher ADMA and SDMA levels and a lower L-arginine/ADMA ratio in infected women.

Changes to manuscript: Lines 137-140

6) *"Additionally, impaired trophoblast invasion and incomplete spiral artery remodeling are observed in both conditions" Please provide a reference for a study that showed incomplete spiral artery remodeling associated with PM.*

Based on reviewer 1's suggestions, we have revised the sentence and included the appropriate reference.

Changes to manuscript: see above

7) *"These pathological changes lead to similar adverse pregnancy outcomes, such as intrauterine growth restriction" Lead or associated with?*

We have revised to state: These pathological changes are associated with similar adverse pregnancy outcomes, such as intrauterine growth restriction, low birthweight, and preterm births.

Changes to manuscript: Lines 151

8) *"A Research and Implementation Agenda for Malaria-Aware Preeclampsia Prevention" It is not clear what new alternative or approaches the authors proposed.*

The first item epidemiological studies, there might be data already collected in some small studies, like the study by Obiri et al in which unfortunately the model wasn't adjusted for SP. But the main issue at hand is that the benefit of IPTp-SP has been described and is well known in preventing PM. Also, the failure in successful implementation of IPTp have been described, here the authors did not propose anything new. ANC visits are supposed to include BP exam and

malaria chemoprevention, how the integrated approach the authors refer to is different? how will that be implemented any better?

Thank you for this important comment. We agree that key components such as IPTp-SP delivery, blood pressure monitoring in antenatal care platforms are well established. We have revised the manuscript to clarify that our proposed approach does not introduce new standalone interventions but rather repositions existing malaria prevention and antenatal care platforms as coordinated tools to jointly study, identify, and mitigate preeclampsia risk.

We now explicitly define “integration” as aligning epidemiologic, mechanistic, and implementation strategies, moving beyond simple co-delivery of services. To reflect this, we have strengthened the agenda by: (1) proposing re-analysis of existing malaria-in-pregnancy trials and cohorts using standardized definitions of hypertensive disorders of pregnancy; (2) incorporating mechanistic endpoints, including placental histopathology and angiogenic biomarkers (e.g., sFlt-1/PlGF and ANGPT2/ANGPT1 ratio), to better understand causal pathways; (3) highlighting comparative analyses of IPTp regimens to evaluate effects beyond parasite clearance; and (4) reframing antenatal care platforms as opportunities for earlier risk identification and stratification, including the use of malaria exposure history and biomarker-informed approaches.

We believe these revisions clarify how the proposed agenda extends beyond current practice by generating new epidemiologic, mechanistic, and implementation insights, rather than duplicating existing strategies.

Changes to manuscript: Lines 226-245

Reviewer #3:

Thank you for the invitation to review this short communication. It is a useful review however it requires a few updates of recent evidence before it is published.

The title

1) *While pre-eclampsia and eclampsia are associated with worse pregnancy outcomes than gestational hypertension it may be work considering hypertensive disorders of pregnancy rather than ‘pre-eclampsia’ alone in the title. It is not just preeclampsia that is*

associated with later onset chronic hypertension and cardiovascular risk. This applies to the manuscript as a whole.

We agree that hypertensive disorders of pregnancy (HDP), more broadly, are associated with adverse pregnancy outcomes and increased long-term cardiovascular risk. In response, we have revised the manuscript to reflect HDP where appropriate, particularly in sections addressing epidemiology, surveillance, and long-term outcomes.

However, we have retained a primary focus on preeclampsia in the title and key mechanistic sections, as the biological pathways central to this viewpoint including placental dysfunction, angiogenic imbalance, and endothelial disruption are most well characterized in preeclampsia and form the basis of the proposed malaria–placental disease link.

Changes to manuscript: Lines 51,84,99, 184,228,267,272

Background

2) *As the manuscript title includes "evidence" i.e. Malaria, Preeclampsia, and Cardiovascular Disease: Evidence and Opportunities; it should therefore give credit to Wickramamasuriya G.A.W., who provided the first descriptions of the link between Pre-eclampsia, Eclampsia and Malaria during his work during malaria epidemics in tea plantations in Ceylon (now Sri-Lanka) (cite Wickramamasuriya G.A.W., Malaria and Ankylostomiasis in the Pregnant Woman, Oxford University Press 1937. London, UK) nearly a century ago.*

This citation has been included.

Changes to manuscript: Line 78

3) *In this sentence: "Malaria in pregnancy remains a major driver of maternal anemia, low birthweight, fetal and neonatal death across much of Africa." Yet reference 6 (systematic review and meta-analysis) includes SGA and Preterm birth which are significantly more informative than LBW, of the harmful impact of malaria. Suggestion to drop LBW and include SGA and PTB.*

Thank you. We have revised the sentence to replace low birthweight with small-for-gestational-age birth and preterm birth

Changes to manuscript: Line 73

4) *.Consider adding the problem of intergenerational effects of malaria and of hypertensive disorders of pregnancy (HDoP) as another reason to prevent them. References could include for malaria (Saito M, et al. Deleterious effects of malaria in pregnancy on the developing fetus: a review on prevention and treatment with antimalarial drugs. The Lancet Child & Adolescent Health, 4, 761-774) and for HDoP, Xiong J, et al. Intergenerational Associations of Hypertensive Disorders of Pregnancy With Offspring Metabolomics: A Systematic Review. Matern Fetal Med. 2025 Jul;7(3):157-165. doi: 10.1097/FM9.0000000000000276. Epub 2025 Mar 17. PMID: 41608203*

As suggested, we have now incorporated a statement in the final section highlighting the intergenerational effects of both malaria in pregnancy and hypertensive disorders of pregnancy, including their potential impact on fetal development and long-term cardiometabolic risk in offspring, with appropriate references.

Changes to manuscript: Line 266-269

Evidence Linking Falciparum Malaria and Preeclampsia (reconsider hypertensive disorders of pregnancy)

5) *.The explanation of reference 10 from SE Asia is not completely correctly presented. True and important to retain: all women were followed from 1st trimester, and the associations were strongest at 14 weeks gestation compared with 28 weeks. Not all women in the SE cohort had falciparum malaria but all women were screened for falciparum and vivax malaria on multiple occasions. Among primigravidae, falciparum malaria was associated with pre-eclampsia/eclampsia (AOR 2.61, 95%CI 1.01–6.79) while among multigravidae, falciparum malaria was associated with gestational hypertension (adjusted odds ratio (AOR) 2.59, 95%CI 1.59–4.23), compared to women with no malaria. And as the argument in this Communications manuscript is on the*

dangers of falciparum and PE you might consider adding that in the same cohort there was no increased risk conferred by vivax malaria, to highlight falciparum.

We have revised the description of the Southeast Asia cohort to more accurately reflect the study design, including first-trimester enrollment and repeated screening for both P. falciparum and P. vivax. We now report the gravidity-specific associations, with falciparum malaria associated with preeclampsia/eclampsia among primigravidae and gestational hypertension among multigravidae, as well as the stronger associations observed earlier in pregnancy. We have also clarified that no increased risk was observed with P. vivax infection, to highlight the specificity of the association with falciparum malaria.

Changes to manuscript: Lines 98-113

6) *Variability of the associations reported to date including in Syst Revs and Metas needs a comment: e.g. ref 6 insignificant assoc with pre-ec, ref 8 risk of pre-ec in MG, ref 9 only 4 studies included and all types of HTN pooled, ref 10 both GH and pre-ec/ec different risk in PG and MG. The quality of the data is important.*

We agree that variability in reported associations and the underlying quality of evidence warrant clarification. We have revised the manuscript to acknowledge heterogeneity across studies, including differences in outcome definitions (e.g., pooling of gestational hypertension and preeclampsia), variation by gravidity, and inconsistencies in reported associations. We also highlight that existing meta-analytic evidence is based on a limited number of studies and often combines hypertensive outcomes, limiting interpretation of condition-specific risks. Additionally, we now emphasize the importance of study design, timing of malaria exposure, and population differences in contributing to variability across findings.

Changes to manuscript: Lines 99-113

7a) Rethink/update the statements on malaria prevention: SP is an antifolate and cannot be given in trimester one when formation of the placenta commences. Indeed, the average gestation of first dose of SP is largely timed, in practice, with the end of placenta formation i.e around 20 weeks (although the WHO recommendations are for earlier uptake i.e. 13 weeks). Hence it will never be administered in a timely way to impact formation of the placental vasculature. 30 years of trying to improve the early and consistent uptake of SP

has not had the impact hoped, not to mention areas where SP is not effective due to drug resistance. The same problems are likely to haunt any role out Aspirin.

Thanks. We agree with the limitations on the timing of sulfadoxine–pyrimethamine (SP) administration which may reduce its ability to influence early placental development also emerging drug resistance affecting its effectiveness in some settings.

We have revised the manuscript to clarify these limitations and included a statement that says: IPTp-SP is initiated after the first trimester due to antifolate safety concerns, limiting its potential to influence early placental development and effectiveness may be limited further by suboptimal uptake and regional drug resistance.

Changes to manuscript: Lines 181-184

7b) Please modify statements on Calcium given new evidence that suggests the purported benefits may be far less significant — and potentially absent —it may not work at all: Cluver CA, Rohwer C, Rohwer AC. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews 2025, Issue 12. Art. No.: CD001059. DOI: 10.1002/14651858.CD001059.pub6. Accessed 28 March 2026.

We have revised the manuscript to reflect this updated evidence and avoid overstating its effectiveness.

Changes to manuscript: Lines 204-207

7c) At least Aspirin could start with SP but unfortunately evidence of daily medications adherence in pregnant women is also needed.

We agree that while aspirin could be initiated alongside IPTp-SP, adherence to daily medication during pregnancy is a key implementation challenge. We have revised the manuscript to acknowledge this consideration in the discussion of preventive strategies.

Changes to manuscript: Lines 207-208

7d) Given the problems i.e. the gestation of implementation (SP, Aspirin) occur after/or too late to completely prevent adverse placentation please consider alternative prevention/s. Pre-conception malaria prevention with long acting antimalarials (ACT with long acting partner) or potentially vaccines (administered with presumptive treatment) to women of child bearing age will be needed to break the linkage of deleterious affects on placentation. See the recently reported trial: Diawara H, et al. Safety and efficacy of PfSPZ Vaccine against malaria in healthy adults and women anticipating pregnancy in Mali: two randomised, double-blind, placebo-controlled, phase 1 and 2 trials. Lancet Infect Dis. 2024 Dec;24(12):1366-1382. doi: 10.1016/S1473-3099(24)00360-8. Epub 2024 Aug 14. PMID: 39153490; PMCID: PMC12117479.

We have revised the manuscript to acknowledge the potential value of earlier preventive strategies, including preconception malaria prevention approaches, long-acting antimalarials and malaria vaccines targeting women of reproductive age

Changes to manuscript: Lines: 198-203

7e) Inevitably, these type of trials (as above) are/will be an excellent source of data for risk of Hypertensive disorders of pregnancy? As long as standardised efforts to record hypertension and test sticks for protein AND linkage between antenatal care records and birth centres are complete.

Thank you for the suggestion. Yes, such trials present an important opportunity to generate high-quality data on hypertensive disorders of pregnancy. We have revised the manuscript to emphasize the need for standardized measurement of blood pressure and proteinuria, as well as robust linkage between antenatal and delivery records, to enable accurate assessment of hypertensive outcomes in these studies.

Changes to manuscript: Lines: 184-190

7f) Advocate for preconception studies (Yanow S, Vinals D Preconception immunisation to prevent pregnancy-associated malaria. The Lancet Infectious Diseases, 2024; 24, 1296-1298

This has been incorporated into the revised manuscript, where we now explicitly discuss preconception malaria prevention approaches, including vaccination of women of reproductive age, supported by emerging evidence. We have also added the suggested reference to strengthen this section.

Changes to manuscript: Lines: 198-203

8)Missing evidence

While the authors outline the requirement for good definitions and diagnostics for malaria and hypertensive disorders of pregnancy the role of nutrition cannot be ignored. In future prospective trials need to account for the rapid changes in the double burden of malnutrition in LMIC and its links to epigenetics (Hoffman DJ, et al., Developmental origins of metabolic diseases. Physiol Rev. 2021 Jul 1;101(3):739-795. doi: 10.1152/physrev.00002.2020. Epub 2020 Dec 3. PMID: 33270534) by recording the most basic of data in pregnancy i.e. at a minimum height and weight so that BMI and GWG can be accounted for. Ideally a measure of gestational diabetes is also needed.

We have revised the manuscript to acknowledge the importance of accounting for the double burden of malnutrition in LMICs and its potential links to epigenetic mechanisms. We now emphasize the need for prospective studies to include basic anthropometric measures (e.g., height, weight, BMI, gestational weight gain) and metabolic assessments such as gestational diabetes to better characterize risk and improve interpretation of findings. The suggested reference has also been incorporated to support this addition.

Changes to manuscript: Lines: 186-190

9) Suggest to recommend/reference free standardised resources e.g. https://intergrowth21.com/course/evidence-based-management-pre-eclampsia-and-eclampsia-interactive-course-health

Suggested reference has been cited

Changes to manuscript: Lines: 186

10)Conclusion

"…building antenatal care models that integrate malaria control and cardiovascular risk reduction, and ensuring that guidelines and policies in endemic regions reflect these needs…" Is not enough. Why? For women in low resource setting the event of the terminal outcomes of pregnancy including: severe gestational hypertension, pre-eclampsia or eclampsia requiring induction, urgent or operative delivery; does not get linked to antenatal events (timing and uptake of SP, use of pre-eclampsia prevention) as it can take place in a completely different part of the health system i.e. hospital rather than clinic.

We have revised the conclusion to emphasize the need for linkage between antenatal and delivery care, recognizing that key pregnancy outcomes often occur in different settings and must be systematically connected to earlier exposures and preventive interventions.

Changes to manuscript: Lines: 266-269

11) 2nd sentence "…However, in high malaria-transmission regions…", reference 10 is not high transmission. Wherever women have a risk of falciparum in early pregnancy there is a risk of HDoP. Suggest caution throughout the manuscript in relation to level of transmission. One might imagine it would be easier to measure outcomes in high transmission areas as data can be accumulated more quickly than in a low transmission settings if there is an effective intervention, but maybe not as immunity, may be a contributing factor i.e. the difference in HDoP by parity.

We have revised the manuscript to reflect this suggestion and to avoid over-specifying transmission intensity. We also added a statement acknowledging that the relationship may vary by transmission intensity, acquired immunity, and parity, which may influence observed associations across settings.

Changes to manuscript: Lines: 277

Response to Editors and Reviewers

Revised Manuscript Title: Evidence and Opportunities for Preeclampsia and Cardiovascular Disease in Malaria Endemic Regions

We thank the editors and reviewers for their additional feedback on our manuscript. We are grateful for the opportunity to further revise our work. We have carefully reviewed each comment and revised the manuscript to address all concerns. Below is a detailed, point-by-point response outlining our changes clarifications.

Reviewers' comments:

1- There is some inconsistency in the nomenclature of Plasmodium falciparum. The authors could standardise it.

These inconsistencies have been noted and amended across the manuscript

Changes to manuscript: Lines 79, 87, 248

2- *In the main text of the article (excluding the abstract), the authors introduce placental malaria as a new term in line 96. It is a bit jarring since there has been, up to this point, no mention that malaria in pregnancy can result in placental malaria. Maybe a connecting sentence before this would suffice.*

Thank you for this helpful suggestion. We have added a transitional sentence before the discussion of placental malaria to clarify that malaria in pregnancy, particularly Plasmodium falciparum infection, can result in placental malaria through placental sequestration of infected erythrocytes.

Changes to manuscript: Lines 97-98

3- Line 152 could cut the words " with antimalarials".

With antimalarials has been deleted

4- The order in which arguments are presented in the "Malaria Prevention as Cardiovascular Disease Prevention" section could be changed to bring the association between preeclampsia

and cardiovascular disease forward to establish a framework that justifies the remaining points in that section.

Thank you. As suggested, we have moved the paragraph on the association between preeclampsia and cardiovascular disease forward.

Changes to manuscript: Lines 159-171