## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Association between interpregnancy interval and pregnancy complications by previous history of complications: a population-based cohort study |
| **AUTHORS** | Gebremedhin, Amanuel Tesfay; Tessema, Gizachew; Regan, Annette; Pereira, G.F |

## VERSION 1 – REVIEW

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| **REVIEWER** | T Ihongbe<br>Virginia Commonwealth University |
| **REVIEW RETURNED** | 12-Feb-2021 |

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| **GENERAL COMMENTS** | This is an interesting paper that seeks to examine whether the association between interpregnancy interval and pregnancy complications is modified by previous obstetric history, specifically, preeclampsia and gestational diabetes. The paper adds to the growing body of literature looking at birth spacing and pregnancy complications. Having said that, there are several shortcomings that the authors need to address. In general, overall manuscript is well written; however, in some sections, there is need to revise for clarity.<br><br>Abstract<br>1. Objective: “To examine if the association between interpregnancy interval (IPI) and pregnancy complications varies by previous experience with these conditions”. The phrase “with these conditions” is quite ambiguous as used. Is it referring to pregnancy complications alone or a combination of IPI and pregnancy complications? The authors should clarify the sentence.<br>2. Conclusions: There is no point in putting the abbreviations for both absolute risk (AR) and relative risks (RR) at the conclusion when they have previously been used in the abstract. If the authors truly wish to include the abbreviations, then include them the first time you state the absolute and relative risks.<br><br>Introduction:<br>3. The citations for the first sentence doesn’t seem adequate. Citation for preeclampsia is from a 1983 paper and that for GDM is from a paper that attempts to estimate global GDM prevalence but faces significant challenges.<br>4. Page 4, line 19: The definition of IPI stated by the authors is too loose. According to the CDC, IPI is the number of months between a live birth and the conception of the next live birth (https://www.cdc.gov/nchs/products/databriefs/db240.htm#:~:text=Interpregnancy%20interval%3A%20The%20number%20of,from%20the%20live%2Dbirth%20interval). The authors should refine the definition of IPI. |

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| | Materials and method<br>5. Page 5, line 11: "…in the period of 1980-2015 in Western Australia (WA). The sentence is grammatically incorrect. Change to either "…in the period between 1980 and 2015…" or "in the period from 1980 to 2015".<br>6. Page 5, line 36: "From total of 487,297 mothers, we sequentially excluded mothers who delivered multiples…". Add "a" after "from". Also, it may be better to say "mothers who had multiple births".<br>7. Page 5, line 44-51: In the text, there seems to be a disconnect between how the authors went from 280,637 eligible mothers to 252,368 mothers with their first two (parity 0, 1) and 96,315 mothers with their first 3 consecutive singleton births (parity 0, 1, 2). Are the 2 groups (parity 0, 1 and parity 0, 1,2) mutually exclusive or not? Although, the supplementary figure does a good job of explaining sample selection, the authors should revise how the study sample was obtained in the text to aid better understanding. Also, if the authors are going to use parity 0, 1, or 2, then they should explicitly clarify the context of use. For example, given that a parity of 0 means that a woman has had no previous live birth, does parity 0 refer to a woman who was previously para 0 before her first birth?<br>8. Page 6, line 5: What was the significance of calculating the IPI prior to exclusions? Also, the authors should state that the unit of IPI was in months.<br>9. No mention is made of an IRB review or exemption. I'm curious as to why?<br>10. Page 6, line 36: "We controlled for potential confounding factors…" The phrase as it is, is quite ambiguous. I would think that you should test potential confounders first to see if they actually confound the association before you control for those confounders. It may be best to say "Potential confounders were measured at…" You can then talk about how confounders were controlled in the analytical section. Also, the abbreviation SES was used before it was defined in full. It should defined in full the first time it's stated.<br>11. From the description of SES given in the SEIFA website, SES was measured at the neighborhood/area level. Why was SES at the neighborhood/area level preferred over SES at the individual level? Also, did the authors examine how much variance the neighborhood SES variable accounted for in the model? Did it account for a significant amount of variance to include it in the model?<br>12. The authors give a list of confounders that were adjusted for in the adjusted model. However, no mention is made as to how these variables were tested to show that they were truly confounding factors before inclusion in the multivariable model. Can the authors expatiate on how confounders were included in the adjusted model?<br>13. The analytical plan isn't sufficiently clear to me. The analysis looks like a multilevel analysis. However, the only statement given to that effect is the use of "Generalized linear models (GLM) fitted using a Poisson distribution with a log link function". No mention is made of how the neighborhood/area-level SES variable was handled in the model.<br>14. In my opinion, the sensitivity analysis that examined whether results differed by the timing of covariate adjustment (i.e., covariates at birth prior to interval versus at time of the outcome) wasn't warranted because many of those variables at the time of the outcome such as marital status, partner change, birth year, SES, temporally were measured after the interpregnancy interval and are less likely to affect the outcome of interest. Also, why adjust for factors that could be caused by length of IPI such as marital status, partner change, birth year? |

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| | Results<br>15. The results section is rather very lengthy. The authors can leave out some findings that can be obtained from the tables and figures.<br><br>Discussion<br>16. Well written. |

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| **REVIEWER** | Michael Johnson Mahande<br>Kilimanjaro Christian Medical University College, Epidemiology & Biostatistics |
| **REVIEW RETURNED** | 15-Feb-2021 |

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| **GENERAL COMMENTS** | The author did not write how they adhered to ethics in this study. Also the author could have simplified the methodological part so reviewers who are not statisticians can understand the methods and reasons for such methodological approach. Since births are clustered within a mother, did the authors consider taking hierarchy into account. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Dr. T Ihongbe, Virginia Commonwealth University

1. This is an interesting paper that seeks to examine whether the association between interpregnancy interval and pregnancy complications is modified by previous obstetric history, specifically, preeclampsia and gestational diabetes. The paper adds to the growing body of literature looking at birth spacing and pregnancy complications. Having said that, there are several shortcomings that the authors need to address. In general, overall manuscript is well written; however, in some sections, there is need to revise for clarity.

Author response: We thank the reviewer for the time taken to review our manuscript.

Abstract
1. Objective: “To examine if the association between interpregnancy interval (IPI) and pregnancy complications varies by previous experience with these conditions”. The phrase “with these conditions” is quite ambiguous as used. Is it referring to pregnancy complications alone or a combination of IPI and pregnancy complications? The authors should clarify the sentence.

Author response: We apologise for the lack of clarity regarding the description of the effect modifier in the objective section. We have now revised to improve clarity and simplifying the interpretation. The phrase ‘these conditions’ is referring to the presence of pregnancy complications in the previous pregnancy and not the combination. For clarity we have summarised the analytic cohort in Table R1 below at response to comment 7.
The objective in the abstract now reads as follow.

“Objective To examine if the association between interpregnancy interval (IPI) and pregnancy complications varies by presence or absence of previous complications.”

2. Conclusions: There is no point in putting the abbreviations for both absolute risk (AR) and relative risks (RR) at the conclusion when they have previously been used in the abstract. If the authors truly

wish to include the abbreviations, then include them the first time you state the absolute and relative risks.

Author response: We thank you for raising our attention to this issue. We have rechecked for similar occurrences throughout the manuscript and corrected accordingly.

Introduction:
3. The citations for the first sentence doesn't seem adequate. Citation for preeclampsia is from a 1983 paper and that for GDM is from a paper that attempts to estimate global GDM prevalence but faces significant challenges.

Author response: thanks for the suggestion. We have now updated the references. We have included the following references in the first paragraph of the introduction section.

1. Buckley BS, Harreiter J, Damm P, et al. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med. 2012;29(7):844-854.
2. Gillon TE, Pels A, von Dadelszen P, MacDonell K, Magee LA. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PloS one. 2014;9(12):e113715.
3. Lawrence RL, Wall CR, Bloomfield FH. Prevalence of gestational diabetes according to commonly used data sources: an observational study. BMC pregnancy and childbirth. 2019;19(1):1-9.
4. Hutcheon JA, Lisonkova S, Joseph K. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best practice & research Clinical obstetrics & gynaecology. 2011;25(4):391-403.

4. Page 4, line 19: The definition of IPI stated by the authors is too loose. According to the CDC, IPI is the number of months between a live birth and the conception of the next live birth (https://www.cdc.gov/nchs/products/databriefs/db240.htm#:~:text=Interpregnancy%20interval%3A%20The%20number%20of,from%20the%20live%2Dbirth%20interval). The authors should refine the definition of IPI.
Author response: We thank you for raising our attention to this issue and for the suggested reference. As the reviewer noted and supplemented in the link, we are aware that the CDC definition for IPI doesn't take in to consideration if the previous pregnancy was stillbirth and compute the interval for the number of months between livebirth and conception of next livebirth, termed as 'livebirth interval,1 which is partly due to nature of the data (National birth certificate) can offer (Thoma et al 2016). 2 Similarly, there are inconsistences in how studies defined IPI. More notably, these differences depend on the use of (1). Date of delivery or conception for either the first or the consecutive pregnancies; (2) status of the pregnancies (i.e., livebirths, stillbirths, miscarriages). Most notably, the approach adopted depends on the nature of the data available. From the literature, the most widely accepted definition (as indicated by the reference suggested by the reviewers is " the time between delivery of a livebirth and the start of the next pregnancy leading to a stillbirth or livebirth" 3 Consistent with this definition, our study defined IPI as the time between the delivery of one pregnancy that resulted in livebirth or stillbirth and the conception of the next pregnancy. Furthermore, for the inclusion of stillbirths in our primary definition, our research team has recently published findings4-6 from the cohort restricting to pregnancies with consecutive livebirths, and found that there were negligible differences in the results which could be attributed to the small (<1%) number of stillbirths in our cohort.

We have now updated the definition to reflect this.

“Interpregnancy interval (IPI) was calculated prior to exclusions as the time between delivery date of the first eligible birth (that resulted in livebirth or stillbirth) during the study period and the estimated conception date of the subsequent pregnancy (date of birth minus gestational age at birth).”

Materials and method

5. Page 5, line 11: “…in the period of 1980-2015 in Western Australia (WA). The sentence is grammatically incorrect. Change to either “…in the period between 1980 and 2015…” or “in the period from 1980 to 2015”.

Author response: Thank you for the suggestion. We have corrected as follow:
“We conducted a population-based, longitudinal cohort study of mothers with at least two consecutive singleton pregnancies in the period between 1980 and 2015 in Western Australia (WA).”

6. Page 5, line 36: “From total of 487,297 mothers, we sequentially excluded mothers who delivered multiples…”. Add “a” after “from”. Also, it may be better to say “mothers who had multiple births”.

Author response: Thank you for the suggestion. The sentence on page 5 now reads as follow:

“From a total of 487,297 mothers, we sequentially excluded mothers who had multiple births; mothers who had only one pregnancy during the study period; mothers whose children’s birth years were inconsistent with the parity and mothers who had missing gestational age, pregnancy outcomes, age, and socio-economic status (SES).”

7. Page 5, line 44-51: In the text, there seems to be a disconnect between how the authors went from 280,637 eligible mothers to 252,368 mothers with their first two (parity 0, 1) and 96,315 mothers with their first 3 consecutive singleton births (parity 0, 1, 2). Are the 2 groups (parity 0, 1 and parity 0, 1,2) mutually exclusive or not? Although, the supplementary figure does a good job of explaining sample selection, the authors should revise how the study sample was obtained in the text to aid better understanding. Also, if the authors are going to use parity 0, 1, or 2, then they should explicitly clarify the context of use. For example, given that a parity of 0 means that a woman has had no previous live birth, does parity 0 refer to a woman who was previously para 0 before her first birth?

Author response: The description of the cohort in the manuscript have now been revised to improve clarity. For simplifying interpretation of our findings, we defined the cohorts to mothers who had their first two consecutive births (parity 0, 1) during the study period as main cohort and a sub-cohort of mothers with three consecutive births (parity 0, 1, and 2) as secondary analyses. We included the results from a cohort of mothers with at least two consecutive births (i.e. at any parity) in the supplementary document (as part of sensitivity analyses; Supplementary Table 2). As is graphically presented in supplementary Figure 1. The eligible mothers with at least two consecutive births during the study period were 280,637 mothers. From these eligible mothers we selected mothers with their first two consecutive births for the parity 0, 1 cohort: and 96,315 mothers with their first three consecutive births during the study period for the parity 0, 1, 2 cohort. We refereed to parity 0 for mothers with no history of previous birth at their first birth, which avoids analysis not to be averaged across women with different levels of parity.

We have re-worded the relevant sentences and have deferred details to the section in the manuscript that describes selection of the study population. We included a Table R1 that summarise this situation below:

Table R1. Summary of cohorts and variable definitions [Please refer to Table R1 in the 'Response to Reviewers_R1'Document attached.

8. Page 6, line 5: What was the significance of calculating the IPI prior to exclusions? Also, the authors should state that the unit of IPI was in months.

Author response: The reason for computing the IPI before exclusion was to avoid exposure misclassification problem that can happen during computing the interval and making sure that all births do have computed IPI before exclusion criteria is applied. For example, if we compute the IPI after exclusions are applied to the cohort, there is higher chance that the computed IPI will be incorrect as there might have been an intervening birth in between (which in this case was excluded as it doesn't fulfil the inclusion criteria). In regard to the unit of measurement, we employed an exact calculation of interval in days and then it was converted to months for simplifying the interpretation. To reflect this, we have updated all of the tables and figures where IPI is mentioned with its unit [interpregnancy interval (months)] including the supplementary tables and figures.

9. No mention is made of an IRB review or exemption. I'm curious as to why?

Author response: Thank you for the comment. Unless the document is trimmed, we have mentioned the ethical clearance with its date of approval at the end of the manuscript [Page 21, line 6-9]. For clarity, we have moved the ethical approval statement to the end of the methods section on page 9 as follow.

"This research was approved by the Human Research Ethics Committee (2016/51) from the Department of Health, WA. The Ethics Committee approval was accepted on 14 September 2016."

10. Page 6, line 36: "We controlled for potential confounding factors…" The phrase as it is, is quite ambiguous. I would think that you should test potential confounders first to see if they actually confound the association before you control for those confounders. It may be best to say "Potential confounders were measured at…" You can then talk about how confounders were controlled in the analytical section. Also, the abbreviation SES was used before it was defined in full. It should defined in full the first time it's stated.

Author response: As per the reviewer suggestion, we have revised the sentences in regard to our potential confounders. The procedures for the variable's selection are now clearly described in the statistical analyses section. We included the following sentence at the methods section (covariates subsection).

"Information on potential confounding factors measured at the birth prior to the interval and including birth year, maternal age, marital status, parity, race/ethnicity and SES was obtained from hospitalisations and perinatal records. "

11. From the description of SES given in the SEIFA website, SES was measured at the neighborhood/area level. Why was SES at the neighborhood/area level preferred over SES at the individual level? Also, did the authors examine how much variance the neighborhood SES variable accounted for in the model? Did it account for a significant amount of variance to include it in the model?

Author response: We thank you the reviewer for this comment. As noticed by the reviewer and our definition of SES in our manuscript on page 6 at covariates subsection, the socio-economic status variable is not measured at individual level, rather at geographical/ area level, which is derived by the Australian Bureau of Statistics (ABS). We agree on the reviewer's concern on the role of SES

measured at geographical area level on predicting health outcomes. However, we also believe that it can be a proxy variable when SES at individual level is not primarily collected or infeasible (in case of administrative data such as ours).7

12. The authors give a list of confounders that were adjusted for in the adjusted model. However, no mention is made as to how these variables were tested to show that they were truly confounding factors before inclusion in the multivariable model. Can the authors expatiate on how confounders were included in the adjusted model?

Author response: We appreciate the need to better describe our variable section procedures and have revised our manuscript accordingly and included a graphical framework (DAG) of the hypothetical pathways on the association between IPI and pregnancy outcome (taking preeclampsia as an example) as supplementary document (supplementary figure 2 and 3).

The statistical analyses section has been updated accordingly.

“Based on existing literature and recent recommendations to represent the potential pathway between IPI and pregnancy outcomes,8 we created a directed acyclic graph (DAG) [Supplementary Figure 2, Supplementary Figure 3]. Covariates fulfilling the minimally sufficient adjustment set were selected. We first tabulated the incidence of each pregnancy complication by IPI (categorised to <6, 6-11, 12-17, 18-23, 24-59, and ≥60 months). We then examined the association between IPI and pregnancy complication (GDM and PE) stratified by previous history of each complication using Generalised linear models (GLM) fitted using a Poisson distribution with a log link function.”

13. The analytical plan isn’t sufficiently clear to me. The analysis looks like a multilevel analysis. However, the only statement given to that effect is the use of “Generalized linear models (GLM) fitted using a Poisson distribution with a log link function”. No mention is made of how the neighborhood/area-level SES variable was handled in the model.

Author response: We thank you for raising this important question. We have tried our best to describe our method of analyses that can be easily understood by all readers (irrespective of their statistical or public health background). As it is indicated in our objective (abstract), we looked at if the associations between IPI and pregnancy complications is modified by presence or absence of these complications in previous pregnancies. We did this by looking at the effect of IPI on each outcome stratified by complication of interest (see Table R1 for details), adjusted for potential confounders (including SES) selected using DAG. SES variable was handled (adjusted) the same as all other potential confounding variables. The analyses is not a ‘multilevel’ but a stratified regression model using PE or GDM as outcome, IPI (modelled using cubic spline) as exposure adjusting for potential confounders, stratified by the effect modifier (e.g., presence or absence of PE in previous pregnancy for PE model). As we hypothesised that the effect of modifier on the association between IPI and each outcome is not same for having two consecutive pregnancies vs three consecutive pregnancies, we presented our results separately throughout the manuscript.

14. In my opinion, the sensitivity analysis that examined whether results differed by the timing of covariate adjustment (i.e., covariates at birth prior to interval versus at time of the outcome) wasn’t warranted because many of those variables at the time of the outcome such as marital status, partner change, birth year, SES, temporally were measured after the interpregnancy interval and are less likely to affect the outcome of interest. Also, why adjust for factors that could be caused by length of IPI such as marital status, partner change, birth year?

Author response: We appreciate the reviewer's concern on the need of sensitivity analyses based on timing of covariate adjustment. We agree on the precautions that should be taken on adjusting factors at the time of outcome as opposed at the birth prior to interval. In the IPI literature majority of studies conducted adjust for either factors measured at each delivery or during the outcome and appeared to be area of a debate for perinatal epidemiologists.9 This was the reason why we opted to look at this scenario and presented our findings as a supplementary. The recent recommendations in this regard suggests that the covariates measured at the time or prior to the initial delivery, rather than during the IPI or subsequent pregnancy to be the most appropriate for inclusion in adjusted analyses. 8

Results
15. The results section is rather very lengthy. The authors can leave out some findings that can be obtained from the tables and figures.

Author response: Thanks for the suggestion. We have updated the results section as per the suggestion

Discussion
16. Well written.
Author response: Thank you for recognising our effort to discuss the pertinent findings.

Reviewer: 2

Dr. Michael Johnson Mahande, Kilimanjaro Christian Medical University College

Comments to the Author:

1. The author did not write how they adhered to ethics in this study. Also the author could have simplified the methodological part so reviewers who are not statisticians can understand the methods and reasons for such methodological approach. Since births are clustered within a mother, did the authors consider taking hierarchy into account?

Author response: We thank you for the comment and suggestion. Given the comment in regard to ethical approval is also mentioned by Reviewer 1, we opted to move the section to methods section. It is now at the end of the methods section on page 9. We have also revisited our methods section including the flow and added texts to simplify for readers. For example, the statistical analyses sub section reads as follow.

"Based on existing literature and recent recommendations to represent the potential pathway between IPI and pregnancy outcomes,8 we created a directed acyclic graph (DAG) [Supplementary Figure 2, Supplementary Figure 3]. Covariates fulfilling the minimally sufficient adjustment set were selected. We first tabulated the incidence of each pregnancy complication by IPI (categorised to <6, 6-11, 12-17, 18-23, 24-59, and ≥60 months). We then examined the association between IPI and pregnancy complication (GDM and PE) stratified by previous history of each complication using Generalised linear models (GLM) fitted using a Poisson distribution with a log link function. We modelled IPI as a continuous variable with a flexible, non-linear approach, restricted cubic splines, with knots placed at 3, 6, 12, 18, 24, 36 and 48 months of IPI. We then estimated absolute risk of each pregnancy complication in 1-month increments of IPI from 3 to 60 months using post estimation calculations.25 For each outcome, the unadjusted model included the IPI spline terms only, and the adjusted model included covariates measured at birth prior to IPI: birth year, SES, marital status, race/ethnicity, and partner change status at recent birth. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th and 95th percentiles (ages 18, 24, 29 and 35). We also adjusted for parity (categorised as nulliparous, parity 1, and 2) for the association between IPI and complications to

ascertain the sensitivity of our results to higher-order parity (Supplementary Table 2). To examine the potential variability of the relationship between IPI and each outcome by previous history of complications, we estimated the predicted absolute risk at the following covariates values: Caucasian, married, average SES, average maternal age and birth year set to 2010 at birth prior to the IPI. We then plotted the predicted risks with 95% confidence intervals (CIs) at 1-month increments of IPI for each outcome stratified by previous history of complications to illustrate the shapes of the risk curves. For tabulated results we presented relative risks (RRs) with 95% CIs at 3, 6, 12, 24, 36, 48 and 60 months of IPI, with 18 months as the reference. Robust (sandwich) variance estimation was used to account for non-independence of 2 or more IPIs per mother."26

Although the non-independence of having tow or more IPIs per mother affects the three consecutive births cohort as well as the cohort with at least two consecutive births, we considered using a robust variance estimation in the regression analysis and is described in the statistical analysis subsection on page 8 as follow.

"Robust (sandwich) variance estimation was used to account for non-independence of 2 or more IPIs per mother"

**VERSION 2 – REVIEW**

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| **REVIEWER** | T Ihongbe<br>Virginia Commonwealth University |
| **REVIEW RETURNED** | 30-Jun-2021 |

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| **GENERAL COMMENTS** | The authors have done a great job in improving the general read of the paper and addressing some of the methodological concerns of the reviewer. However, I am not satisfied with the way the area level SES variable was handled in the model. Based on the description of the SES variable on the SEIFA website, it is clearly a higher order (level 2) variable. Including it in the model as a level 1 variable to act as a proxy for SES is not appropriate. Effectively, the independence assumption is violated, as the SES of women within the same area level is similar to each other than for women in other areas levels. If the authors are going to include the area level SES variable, then, it should be handled appropriately. |

**VERSION 2 – AUTHOR RESPONSE**

**RESPONSE TO REVIEWERS' COMMENTS**

**Reviewer Comments to Author**

**Reviewer: 1**

Dr. T Ihongbe, Virginia Commonwealth University

The authors have done a great job in improving the general read of the paper and addressing some of the methodological concerns of the reviewer. However, I am not satisfied with the way the area level SES variable was handled in the model. Based on the description of the SES variable on the SEIFA

website, it is clearly a higher order (level 2) variable. Including it in the model as a level 1 variable to act as a proxy for SES is not appropriate. Effectively, the independence assumption is violated, as the SES of women within the same area level is similar to each other than for women in other areas levels. If the authors are going to include the area level SES variable, then, it should be handled appropriately.

**Author response:**

We thank you the reviewer for the time taken to review our manuscript and acknowledging our effort. We absolutely agree with the reviewer's concern that area-level SES measure may not be suitable proxy for individual-level SES because of potential disagreement and contextual effects of neighbourhood environments on health outcomes independent of individual-level SES. However, individual-level SES factors are absent from much health administrative data such as ours, resulting in extensive use of area-level measure. This is also a fairly common method used by other countries for population-based studies.[1-4]

However, as per the reviewer's suggestion we have included two more models

1. GLM model not adjusted for area-level SES and
2. Multi-level mixed model regression considering SES as level-2 variable.

The effect estimates and the model parameters for each model is presented in **Table R1** below. We have also reported the ICC for the multi-level mixed effect model which helps to answer the question of the total variation in the outcome variable (PE or GDM), how much is accounted for by the variation among the higher order (unit) variable (area level SES in this case). The multi-level mixed effect model indicate that the ICC values are considerably low (<0.008). We opted to present the original analysis, as use of the multi-level mixed method changes neither the effect estimates nor the conclusion.

The Table R1 below presents the adjusted RR (95% CI) of PE and GDM according to IPI stratified by pregnancy complications at first pregnancy for others with their first two consecutive births during the study period for each of the three scenarios.

1. Generalised Linear Model (GLM) model adjusted for SEIFA
2. GLM not adjusted for SEIFA
3. Multi-level Mixed model (MEGLM) considering SEIFA measurements as level-2 variable.

**Table R1. Adjusted Relative Risk (RRs) of pregnancy complications according to IPI stratified by pregnancy complication at first pregnancy for mothers with their first two consecutive births during the study period (n=252,368 mothers); sensitivity analysis for fitting SES**

| | | Interpregnancy interval (months): Relative risk (95% CI) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Outcome** | | **3** | **6** | **12** | **18** | **24** | **36** | **48** | **60** | |
| **Preeclampsia** | | | | | | | | | | |
| **Model** | **Previous PE** | | | | | | | | | **ICC** |
| GLM¶ | RR (95% CI) | 1.09 (0.94-1.25) | 0.99 (0.89-1.09) | 0.93 (0.85-1.03) | 1 (Reference) | 0.97 (0.90-1.05) | 1.04 (0.95-1.13) | 1.06 (0.98-1.16) | 1.06 (0.98-1.15) | |
| GLM§ | RR (95% CI) | 1.09 (0.95-1.26) | 0.99 (0.90-1.09) | 0.93 (0.85-1.03) | 1 (Reference) | 0.97 (0.90-1.05) | 1.04 (0.95-1.13) | 1.06 (0.98-1.16) | 1.06 (0.98-1.15) | |
| Multi-level mixed¥ | RR (95% CI) | 1.09 (0.99-1.21) | 0.99 (0.92-1.07) | 0.93 (0.88-1.00) | 1 (Reference) | 0.97 (0.86-1.10) | 1.04 (0.94-1.15) | 1.06 (0.99-1.14) | 1.06 (1.00-1.13) | 0.0000 |
| | **No previous PE** | | | | | | | | | |
| GLM¶ | RR (95% CI) | 1.24 (1.07-1.43) | 1.0 (0.90-1.11) | 0.9 (0.81-0.99) | 1 (Reference) | 1.04 (0.96-1.13) | 1.23 (1.13-1.35) | 1.34 (1.23-1.46) | 1.40 (1.29-1.53) | |
| GLM§ | RR (95% CI) | 1.26 (1.09-1.45) | 1.0 (0.90-1.12) | 0.9 (0.81-0.99) | 1 (Reference) | 1.04 (0.96-1.13) | 1.24 (1.14-1.35) | 1.35 (1.24-1.47) | 1.41 (1.29-1.53) | |
| Multi-level mixed¥ | RR (95% CI) | 1.24 (0.89-1.73) | 1.0 (0.82-1.21) | 0.9 (0.79-1.02) | 1 (Reference) | 1.04 (0.89-1.21) | 1.23 (1.03-1.48) | 1.34 (1.13-1.59) | 1.40 (1.18-1.66) | 0.0032 |
| **Gestational diabetes** | | | | | | | | | | |
| | **Previous GDM** | | | | | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|
| GLM¶ | RR (95% CI) | 1.11 (0.95-1.29) | 0.87 (0.78-0.97) | 0.94 (0.85-1.04) | 1 (Reference) | 0.96 (0.88-1.04) | 1.07 (0.98-1.18) | 1.14 (1.05-1.25) | 1.18 (1.07-1.29) | |
| GLM§ | RR (95% CI) | 1.12 (0.96-1.30) | 0.88 (0.79-0.98) | 0.94 (0.85-1.04) | 1 (Reference) | 0.96 (0.88-1.05) | 1.08 (0.98-1.18) | 1.14 (1.05-1.25) | 1.18 (1.07-1.29) | |
| Multi-level mixed¥ | RR (95% CI) | 1.12 (0.92-1.35) | 0.88 (0.83-0.93) | 0.94 (0.87-1.02) | 1 (Reference) | 0.96 (0.87-1.07) | 1.08 (1.00-1.15) | 1.14 (1.06-1.24) | 1.18 (1.10-1.26) | 0.0000 |
| | **No previous GDM** | | | | | | | | | |
| GLM¶ | RR (95% CI) | 1.00 (0.85-1.16) | 0.87 (0.78-0.97) | 0.87 (0.79-0.96) | 1 (Reference) | 1.20 (1.11-1.29) | 1.75 (1.62-1.90) | 2.18 (2.01-2.35) | 2.58 (2.38-2.79) | |
| GLM§ | RR (95% CI) | 1.02 (0.88-1.20) | 0.89 (0.79-0.99) | 0.87 (0.79-0.96) | 1 (Reference) | 1.20 (1.11-1.29) | 1.77 (1.64-1.92) | 2.2 (2.04-2.38) | 2.61 (2.42-2.81) | |
| Multi-level mixed¥ | RR (95% CI) | 1.00 (0.81-1.24) | 0.87 (0.79-0.97) | 0.87 (0.82-0.91) | 1 (Reference) | 1.2 (1.13-1.28) | 1.75 (1.64-1.88) | 2.18 (2.07-2.29) | 2.58 (2.46-2.70) | 0.0079 |

Interpregnancy interval (IPI) was modelled using restricted cubic splines with knots placed at 3, 6, 12, 18, 24, 36, 48 months of interpregnancy interval. Models were adjusted for maternal age, SES, birth year, ethnicity, marital status at birth prior to IPI and partner change at recent birth with 18-month of IPI as reference. Maternal age was modelled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles (ages 18, 24, 29, and 35); ¶Generalized linear (GLM) model adjusted for SES; §Generalized linear (GLM) model not adjusted for SES; ¥Multi-level mixed model with SES as second - level variable; ICC: Interclass Correlation Coefficient; *PE: preeclampsia; GDM: gestational diabetes*

## VERSION 3 – REVIEW

| | |
|---|---|
| **REVIEWER** | T Ihongbe<br>Virginia Commonwealth University |
| **REVIEW RETURNED** | 27-Sep-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | It's nice of the authors to present the findings from the 3 models shown in Table R1. Based on the table results, I agree with the authors' explanation to use the GLM model using SEIFA (i.e., SES) as a proxy for SES. However, to provide clarity to readers who may also wonder why area-level SES is being utilized this way, it will be best to state in the main text that "since the intraclass coefficient was considerably low and the confidence intervals of the estimates were not significantly changed in the multilevel model, the GLM model using SEIFA (i.e., SES) as a proxy for SES was utilized." |

## VERSION 3 – AUTHOR RESPONSE

**Reviewer Comments to Author**

**Reviewer: 1**

Dr. T Ihongbe, Virginia Commonwealth University

Comments to the Author:
It's nice of the authors to present the findings from the 3 models shown in Table R1. Based on the table results, I agree with the authors' explanation to use the GLM model using SEIFA (i.e., SES) as a proxy for SES. However, to provide clarity to readers who may also wonder why area-level SES is being utilized this way, it will be best to state in the main text that "since the intraclass coefficient was considerably low and the confidence intervals of the estimates were not significantly changed in the multilevel model, the GLM model using SEIFA (i.e., SES) as a proxy for SES was utilized."

**Author response:** We thank the reviewer for the time taken to review our manuscript. As suggested, we have included the following text in the main document on page 6:

*"Socio-economic status was derived by the Australian Bureau of Statistics as Socio Economic Indexes for Areas (SEIFA) at a geographic area for the maternal residence at the time of birth,[23] and categorised into quintiles.*

And in the statistical analysis sub section on page 7:

*"Since the intraclass coefficient was considerably low and the confidence intervals of the estimates were not significantly changed in the multilevel model, the GLM model using SEIFA as a proxy for SES was utilized.*