OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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Date: Jul 09, 2021
To: "Danielle M. Panelli" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1202

RE: Manuscript Number ONG-21-1202

Epilepsy in pregnancy: understanding the risk of severe maternal morbidity

Dear Dr. Panelli:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 30, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: ONG-21-1202

This is an observational study to evaluate the risk of SMM in pregnant women with epilepsy.
Main issues:
1- Not sure if there is new information in this study. Per references included in the paper, there are evidence of higher complications including mortality from prior report. How deos this study affect the care of women with known epilepsy during pregnancy?
2- The data is from 2007-2012, please explain why this was not expended to date to reflect the current clinical practice? Especially with rare outcomes, it might make sense to include more data from the last 9 years.

Comments:
1- Line 94: prevalence is rate and is different that absolute number of cases, please report the prevalence as a % of the population.
2- Line 211: " nearest neighbor matching" Please clarify the distance used for the nearest neighbor matching and the criteria used for matching.
3- Line 224: "patients with epilepsy were more likely to be younger, Hispanic, have high BMI at delivery, have not completed college and have commercial insurance". Are those factors were included in the propensity score model used for constructing the propensity score.
4- Line 239: "4.3% vs 1.4%". Please report the unadjusted OR before reporting the adjusted OR at least for the primary outcome which is the overall SMM and the non-transfusion SMM.
5- Is there more risk for SMM observed in certain subgroups of epilepsy?
6- Line 271: Please add to the text in the results the OR for non-transfusion SMM.
7- Line 329: What would you do differently for the next pregnant women with epilepsy?

Reviewer #2: 1. The study type is listed as "observational cohort". If I have it right, this research was done retrospectively. Would it be better to specify that -- i.e., "TROHOC" study, if you will ? It would give the private practitioners and learning readers a better sense of where the study would fit in the scheme of study types and risk for biases.

2. The Confounding Variables section (in Methods) is very confusing. I had to read it several times to begin to understand

what you did. Would you be able to rephrase it for the average reader out there (i.e., "dumb it down" for me) ?

3. After adjusting for the a priori identified confounding variables and the comorbidity score, the resultant ORs almost all fall into Grimes and Schulz's (Obstet Gynecol 2012) zone of potential bias, leaving only a few ORs in their zone of potential interest (i.e., those for generalized epilepsy). How do you answer this ?

4. When looking at the Hill criteria to establish causation, these data fail on most of the 9 separate criteria. Perhaps most of all the "plausibility" criterion. How would you try to mechanistically explain that half of all SMMs that are blood loss / transfusion related ? If this is largely tied to the slightly higher Caesarean risk for epileptics, then the battle is lost, no ?

5. Is a PROspective cohort study planned ?

Reviewer #3: In this observational study, the authors examined the impact/effect of epilepsy on severe maternal morbidity (SMM) using the SMM indicators from by the CDC. Between 2007 and 2012, out of over 2.6M births, 8145 were to women with epilepsy. The main findings were a significantly higher association between epilepsy and SMM both transfusion and non-transfusion SMM even after adjustments for co-morbidities. The author concluded that SMM was significantly increased in patients with epilepsy and that SMM indicators across all organ systems contributed to this increase. These observations provide useful confirmatory data on what is known and perhaps emphasizes the need for more research into why this is indeed the case.
Introduction:
1. In line 103, reference is made to 'rarity of outcomes studied' being a possible reason for the conflicting evidence of increased pregnancy complications. Would it be possible to identify some of these outcomes that are considered rare? Are these rare in epileptics or in general?
2. Please provide a definition of what is considered severe maternal morbidity composite - lines 104-105
3. With regards to referencing the CDC SMM Indicators, I would suggest reference 12 is included in the introductory paragraph as that's is where these indicators are explained in details.
METHODS
1. This study is described as an observational cohort. Are cohort studies not by themselves observational? I will suggest dropping the cohort.
2. Was this a prospective or retrospective study? This is not clear. The authors should state very clearly what this was - I am guessing it was a retrospective study.
3. Presumably SMM was compared between those with epilepsy and the general obstetric population. If this was the case will this be considered a justifiable comparison? If various confounders were taken into analysis then this would be acceptable but if this was not, then possible biased could have been introduced in the analysis.
4. Epilepsy was classified as generalized, focal and other types - lines 138-140. Could the other types be given in brackets after the other types for the interest of this reader and presumably others?
5. Lines 151-152. Not very clear what 'a patient with generalized epilepsy and epilepsy in complicating pregnancy' mean. It seems as if these are two different conditions. Please clarify or rephrase.
6. In the outcomes the primary one was SMM (line 155) - presumably this is composite SMM rather than just SMM as stated later at line 157. Would it not be useful to add secondary outcomes at line 158 or somewhere in this section?
7. Lines 163-165 - see comment above on comparisons.
8. In the organ system groups there is 'hemorrhage SMM' and 'transfusion SMM'. Presumably these are inter-related?
9. In the confounding variables, there is no mention of previous obstetric factors. It is recognized that some of the SMM indicators have a high recurrent or increase the risk of recurrence. Why was this not included in the analyses? It may well be that these data were not available. If that is the case, a comment should be made to this effect.
RESULTS
1. These are in general well presented. Some of the tables are too busy and it may be better to reduce the variables and emphasize those with significance since he narrative states these are well.
2. Figure 2 does not really add much to what is Table 5. Furthermore, when you combined the figures for cardiac and pulmonary SNMM these add to less than what is presented in the Figure. The other variables match those in the Figure.
DISCUSSION:
1. This is relevant and deals with the important issues in the study.
2. The very high preterm delivery rate in those with epilepsy compared to the general population highlights the point raised above about appropriate controls. A preterm delivery rate of 41.9% is very high indeed. Were there any data on the degree of control of the epilepsy and if so were these included in the analyses?
3. While there are comments on the strengths of the study, no attempt is made to highlight the limitations. I would like to see some of these especially if the data were collected retrospectively
REFERENCES
These are up-to-date although do not conform to the style for the Journal

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Lines 128-130: Of all births in California during the years of this study, how many N(%) were not linked or otherwise excluded?

lines 211-213, 267-269, & Supplementary Table: Need to include in supplemental material the results of the matching process, including the N from each group after the match, the closeness of the match for all the relevant variables and replication of Table 3, to compare with its output based on multivariable adjustment. Suggest including in main text, if possible.

Table 1: Need units for BMI.

lines 332-333: To put the increased risk in context, how would epilepsy as a risk factor for SMM (both in absolute and relative terms), compare with other known risk factors for SMM? Might be useful as another Table, even though it may not be modifiable.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
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The following authors need to complete the form:

Thomas F. McElrath (tmcelrath@bwh.harvard.edu)
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3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was

convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

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* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
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* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
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9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Please spell out "SMM" throughout your manuscript, except in tables and figures.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

13. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

14. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

15. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

16. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

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* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 30, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

RESPONSE TO REVIEW
MANUSCRIPT ID: ONG-21-1202
*Note: line references in Reviewer comments refer to original manuscript, line references in responses refer to revised manuscript with changes accepted.

REVIEWER #1: This is an observational study to evaluate the risk of SMM in pregnant women with epilepsy.

1. Not sure if there is new information in this study. Per references included in the paper, there are evidence of higher complications including mortality from prior report. How does this study affect the care of women with known epilepsy during pregnancy?

We agree with the Reviewer that there have been previously published studies demonstrating increases in complications such as preeclampsia and maternal mortality among people with epilepsy. However, as we describe in our introduction (Lines 101-104), there have also been studies published questioning these risks. These conflicting reports leave ambiguity in how best to manage pregnancies for these patients, and we believe our results help fill this knowledge gap by highlighting which people with epilepsy are at the highest risk of severe maternal morbidity. Unique aspects of our study include our comparison between different epilepsy subtypes, as well as our interrogation of individual severe maternal morbidity components that contributed to the increased overall risk increase among people with epilepsy. With our data, we hope clinicians can be reassured that the absolute risk of severe maternal morbidity is low for people with epilepsy, but that the relative risk is increased. Measures to reduce postpartum hemorrhage or monitor for cardiopulmonary events in the peripartum period are two ways in which clinicians might change practice based on our results.

2. The data is from 2007-2012, please explain why this was not expended to date to reflect the current clinical practice? Especially with rare outcomes, it might make sense to include more data from the last 9 years.

We agree with the Reviewer that expanding the study timeframe would increase our sample size. Unfortunately, the California Office of Statewide Health Planning and Development stopped linking patient discharge data with vital records (live birth and fetal death certificates) after 2012. In addition, given the differences in epilepsy coding between ICD-9 and ICD-10, we believe grouping populations with these codes could result in inconsistencies during the coding transition. Though we don't have reason to believe the relationship between epilepsy and SMM has meaningfully changed since 2012, we hope to further evaluate trends over time in future research focused solely on the ICD-10 era when the data become available.

3. Line 94: prevalence is rate and is different that absolute number of cases, please report the prevalence as a % of the population.

We appreciate this Reviewer comment and have changed the line as suggested.

> *Lines 94-96: The number of people with epilepsy in the U.S. is rising, increasing from 2.3 million in 2010 to 3 million in 2015.[1,2] Approximately 24,000 patients with epilepsy deliver annually, accounting for 0.3-0.5% of all births.[3,4]*

4. Line 211: " nearest neighbor matching" Please clarify the distance used for the nearest neighbor matching and the criteria used for matching.

*We performed greedy nearest neighbor matching using "method_nearest" in the MatchIt package in R. A distance is computed between each treated unit and each control unit, and, one by one, each treated unit is assigned a control unit as a match. The matching is "greedy" in the sense that there is no action taken to optimize an overall criterion; each match is selected without considering the other matches that may occur subsequently. More information is available: Ho DE, Imai K, King G, Stuart EA (2011). "MatchIt: Nonparametric Preprocessing for Parametric Causal Inference." Journal of Statistical Software, **42**(8), 1–28. https://www.jstatsoft.org/v42/i08/. We have added the following clarification to the Methods section.*

Lines 232-244: Lastly, as an assessment of the robustness of our results and analytical decisions, propensity-score matching was done to analyze the association between epilepsy and severe maternal morbidity and non-transfusion severe maternal morbidity. We used greedy nearest neighbor matching with "method nearest" in the MatchIt package in R, which matches patients with and without epilepsy based on the closest propensity score in order to optimally balance covariates between groups. In this analysis, a distance is computed between each treated unit and each control unit, and, one by one, each treated unit is assigned a control unit as a match. The matching is "greedy" in the sense that there is no action taken to optimize an overall criterion; each match is selected without considering the other matches that may occur subsequently.[5] *We re-ran Models 2 and 3 using propensity score matching for both severe maternal morbidity and non-transfusion severe maternal morbidity, using the same covariates noted above.*

5. Line 224: "patients with epilepsy were more likely to be younger, Hispanic, have high BMI at delivery, have not completed college and have commercial insurance". Are those factors were included in the propensity score model used for constructing the propensity score.

Maternal age, race/ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity were included in the original propensity score model as well as the multivariable logistic regression in Model 2, which was the primary analysis for the study. BMI is a component of the obstetric comorbidity score, which was added to the multivariable logistic regression to generate Model 3. Originally we had only replicated Model 2 with propensity score matching, but given this comment we have revised the propensity score analysis so that both Model 2 and Model 3 have been replicated using propensity-matching. We have clarified this in our Methods section as shown below and in the Appendix.

Lines 242-244: We re-ran Models 2 and 3 using propensity score matching for both severe maternal morbidity and non-transfusion severe maternal morbidity, using the same covariates noted above.

Appendix Tables: See Statistical Reviewer, Comment 2 response below

6. Line 239: "4.3% vs 1.4%". Please report the unadjusted OR before reporting the adjusted OR at least for the primary outcome which is the overall SMM and the non-transfusion SMM.

We have made the suggested changes to the Results section as shown below.

Lines 267-272: The risk of severe maternal morbidity was significantly increased in births with maternal epilepsy compared to births without epilepsy (4.3% versus 1.4%, crude odds ratio [OR] 3.10 [95% confidence interval (CI) 2.79-3.45], adjusted OR [aOR] 2.91 [95% CI 2.61-3.24] Table 3) as was non-transfusion severe maternal morbidity (2.9% versus 0.7%, crude OR 4.52 [95% CI 3.97-5.15], aOR 4.16 [95% CI 3.65-4.75], Table 4).

7. Is there more risk for SMM observed in certain subgroups of epilepsy?

Table 3 and Table 4 demonstrate the crude and adjusted risks of severe maternal morbidity and non-transfusion severe maternal morbidity broken down by epilepsy subgroups based on ICD-9 codes. The groups were defined as described in the Methods section (lines 136-157) as generalized epilepsy, focal epilepsy and other less specified epilepsies, unspecified epilepsy complicating pregnancy, childbirth, or the puerperium, and convulsions. Due to small numbers for each specific ICD-9 epilepsy diagnosis code and the wide variety of possible codes available, it would be difficult to compare outcomes if these groups were further divided into more subtypes. For this reason, we condensed the groups in this way with input from Dr. Meador who has clinical expertise in this area. The risks shown in Table 3 and Table 4 are described in the Results section as shown below. We are happy to further expand on this in the text if further clarification is needed.

Lines 272-281: When comparing severe maternal morbidity by epilepsy subtype, generalized epilepsy was associated with the highest risk of both severe maternal morbidity (aOR 5.32, 95% CI 3.97-7.14) and non-transfusion severe maternal morbidity (aOR 8.83, 95% CI 6.34-12.89). Focal or other less specified epilepsy subtypes were also associated with significantly increased risk of both severe maternal morbidity (aOR 2.61, 95% CI 2.29-2.97) and non-transfusion severe maternal morbidity (aOR 3.78, 95% CI 3.21-4.40). When examining individual codes for unspecified epilepsy, severe maternal morbidity remained similarly increased for unspecified epilepsy complicating pregnancy, childbirth, or the puerperium (aOR 3.23, 95% CI 1.88-5.54) as well as for convulsions (aOR 3.20, 95% CI 2.38-4.31).

8. Line 271: Please add to the text in the results the OR for non-transfusion SMM.

This was added as shown below:

Lines 266-272: The risk of severe maternal morbidity was significantly increased in births with maternal epilepsy compared to births without epilepsy (4.3% versus 1.4%, crude odds ratio [OR] 3.10 [95% confidence interval (CI) 2.79-3.45], adjusted OR [aOR] 2.91 [95% CI 2.61-3.24] Table 3) as was non-transfusion severe maternal morbidity (2.9% versus 0.7%, crude OR 4.52 [95% CI 3.97-5.15], aOR 4.16 [95% CI 3.65-4.75], Table 4).

9. Line 329: What would you do differently for the next pregnant women with epilepsy?

We appreciate this Reviewer comment, as we hope this is the take-home message for our manuscript. As described in our response to Reviewer 1, Comment 1 above, the results from our study emphasize the contribution of transfusion, hemorrhage, and cardiopulmonary events to severe maternal morbidity and highlight which people with

epilepsy might be at highest risk of these complications. This has been added to the Discussion.

Lines 310-312: Overall, our findings emphasize the contribution of hemorrhage to severe maternal morbidity for patients with epilepsy, highlight who might be at highest risk of complications, and reaffirm the importance of ongoing research in this area.

REVIEWER #2:

1. The study type is listed as "observational cohort". If I have it right, this research was done retrospectively. Would it be better to specify that -- i.e., "TROHOC" study, if you will ? It would give the private practitioners and learning readers a better sense of where the study would fit in the scheme of study types and risk for biases.

The Reviewer is correct that, from the study team vantage point, the research was done retrospectively. However, we prefer not to refer to the study design itself as retrospective since that terminology calls to mind the issue of recall bias associated with assessment of an exposure after the occurrence of an outcome, as in a case-control study. For this study, the exposure and outcome variables were ascertained using ICD-9 codes which were utilized in real time. For this reason, we initially chose to call this an "observational cohort". However, given this comment as well as Reviewer 3, Comment 5, we have changed the text to describe this as a cohort study and clarify that the data were analyzed retrospectively.

Lines 51-52: We retrospectively examined severe maternal morbidity using linked birth certificate and maternal hospital discharge records in California between 2007 and 2012.

Lines 118-120: This was a cohort study of pregnancies in California between 2007 and 2012 to assess risks of maternal epilepsy in pregnancy. Data were analyzed retrospectively.

2. The Confounding Variables section (in Methods) is very confusing. I had to read it several times to begin to understand what you did. Would you be able to rephrase it for the average reader out there (i.e., "dumb it down" for me) ?

We are grateful to the Reviewer for this comment, and have attempted to clarify the confounding variables and statistical analysis sections of the manuscript. Since several models were run, we attempted to simplify this section by assigning each model a number (e.g. Model 1 for crude logistic regression, Model 2 for multivariable logistic regression, and Model 3 for multivariable logistic regression including obstetric comorbidity score as a covariate). The Methods section has been revised as shown below in order to address this comment.

(i) Lines 189-202: Potential confounders were selected a priori based on prior literature on severe maternal morbidity and epilepsy and causal diagrams.[4,6,7] *These included maternal age, race or ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity (which were included as covariates in multivariable logistic regression Model 2, see below). Race or ethnicity were obtained from the birth certificate, where it is self-reported by the patient. This approach has been previously validated using California birth certificate data.*[8] *We additionally identified comorbidities, such*

as chronic cardiovascular disease, as potential confounders or mediators of the association between epilepsy and severe maternal morbidity. Given this, we planned a separate multivariable logistic regression model to also account for the role comorbidities might be playing in severe maternal morbidity for patients with epilepsy. To do so, comorbidities were added as a covariate to the aforementioned Model 2 to create Model 3. Comorbidities were defined using a previously developed expanded obstetric comorbidity scoring system to create a comorbidity composite.[6]

(ii) Lines 222-246: A series of additional analyses were then conducted to minimize potential bias. First, multivariable logistic regression models (Model 2) were adjusted for the confounding variables listed above (maternal age, race or ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity). Secondly, the obstetric comorbidity score described above was added as a covariate to Model 2 to generate Model 3. These models were run separately in the event that comorbidities served as mediators rather than confounders of the association between epilepsy and severe maternal morbidity. Next, multivariable logistic regression models were used to compare the odds of each of the 21 CDC severe maternal morbidity indicators between pregnancies with and without maternal epilepsy, adjusted for the same potential confounders listed above in Model 2. Lastly, as an assessment of the robustness of our results and analytical decisions, propensity-score matching was done to analyze the association between epilepsy and severe maternal morbidity and non-transfusion severe maternal morbidity. We used greedy nearest neighbor matching with "method nearest" in the MatchIt package in R, which matches patients with and without epilepsy based on the closest propensity score in order to optimally balance covariates between groups. In this analysis, a distance is computed between each treated unit and each control unit, and, one by one, each treated unit is assigned a control unit as a match. The matching is "greedy" in the sense that there is no action taken to optimize an overall criterion; each match is selected without considering the other matches that may occur subsequently.[5] *We re-ran Models 2 and 3 using propensity score matching for both severe maternal morbidity and non-transfusion severe maternal morbidity, using the same covariates noted above. Significance was set to a two-tailed alpha=0.05. All statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.6.1 (Vienna, Austria).*

3. After adjusting for the a priori identified confounding variables and the comorbidity score, the resultant ORs almost all fall into Grimes and Schulz's (Obstet Gynecol 2012) zone of potential bias, leaving only a few ORs in their zone of potential interest (i.e., those for generalized epilepsy). How do you answer this ?

We appreciate the Reviewer's mention of Grimes and Schulz's zones of potential bias which is relevant when considering epidemiologic data. In their paper, Grimes and Schulz report an OR of 2.0 or greater to be the start of the zone of potential interest for a cohort study. As shown in Tables 3 and 4, all but one of our adjusted ORs in Model 3 are greater than 2.0. In Table 5, all adjusted ORs are greater than 2.0. In addition, the ORs we found in our analysis are higher than the ORs for other conditions such as chronic

hypertension or connective tissue or autoimmune disease.[6] *We believe this further underscores the robustness of our findings.*

4. When looking at the Hill criteria to establish causation, these data fail on most of the 9 separate criteria. Perhaps most of all the "plausibility" criterion. How would you try to mechanistically explain that half of all SMMs that are blood loss / transfusion related ? If this is largely tied to the slightly higher Caesarean risk for epileptics, then the battle is lost, no ?

We have attempted to address these criteria in as many ways as we could with our study. As discussed in response to Reviewer 2, Comment 3 above, many of the associations we identified have ORs greater than 2 which demonstrates ***strength****.* ***Consistency*** *with other available literature is somewhat controversial for the reasons discussed in our Introduction, which is what actually prompted us to pursue this research. That being said, epilepsy has been associated with adverse birth outcomes so there is consistency between our results and what is available in the literature.*[3,4,9] ***Temporal sequence*** *was addresed by limiting our definition of epilepsy only to those who had a code for epilepsy marked present on admission which would presumably be prior to SMM occurrence. Furthermore, we excluded people with codes for both convulsions and eclampsia from the study to avoid misclassification of the exposure which would also affect temporal sequence. In terms of* ***dose response****, we report the findings of our primary analysis broken down by epilepsy subtype with generalized epilepsy theoretically representing the most severe type of epilepsy. In accordance with dose response expectations, people with generalized epilepsy were at greater risk of SMM than people with other types of epilepsy. We discuss* ***biologic plausibility*** *of the association between epilepsy and SMM in our Discussion section; poorly controlled seizures, trauma from falls, an increased inflammatory state, or even AED use could all potentially underlie the association between epilepsy and SMM.* ***Experimental evidence, coherence, and analogy*** *do not seem readily applicable to our data, but we are happy to incorporate any suggestions from the Reviewer or Editors on how to address these in our study.*

To address the second point of this Reviewer comment, we agree that the large contribution of hemorrhage and transfusion to SMM, as well as the increased cesarean rate, among people with epilepsy was striking in our results. As other studies have shown cesarean birth rates can be modifiable[10]*, our study provides a possible avenue to pursue future research in this area. In fact, our team is using these results to develop a follow up study investigating why cesarean births are increased in this population. We hope that our results may be hypothesis-generating for others pursuing work in this field.*

5. Is a PROspective cohort study planned?

While our large epidemiologic study provides the benefit of analyzing rare events among people with epilepsy, we agree with the Reviewer that a prospective cohort study would likely provide more granular data to corroborate our results. That being said, our findings demonstrate trends on a population-level that can help direct future research in smaller cohorts. In fact, our co-authors are leading a prospective national cohort study for this purpose.

REVIEWER #3: In this observational study, the authors examined the impact/effect of epilepsy on severe maternal morbidity (SMM) using the SMM indicators from by the CDC. Between 2007 and 2012, out of over 2.6M births, 8145 were to women with epilepsy. The main findings were a significantly higher association between epilepsy and SMM both transfusion and non-transfusion SMM even after adjustments for co-morbidities. The author concluded that SMM was significantly increased in patients with epilepsy and that SMM indicators across all organ systems contributed to this increase. These observations provide useful confirmatory data on what is known and perhaps emphasizes the need for more research into why this is indeed the case.

1. In line 103, reference is made to 'rarity of outcomes studied' being a possible reason for the conflicting evidence of increased pregnancy complications. Would it be possible to identify some of these outcomes that are considered rare? Are these rare in epileptics or in general?

We have changed the phrasing for this line in the Introduction as shown below to provide eclampsia as one example of a rare outcome studied among people with epilepsy. The purpose of this sentence is to set up the introduction of the severe maternal morbidity measure, so "rare complications" was added to the following sentence as shown below.

Lines 102-104: This may be due to variability in seizure type and control, or to the rarity of individual outcomes, such as eclampsia, which have been studied. In an attempt to understand rare complications that might contribute to maternal mortality, the severe maternal morbidity (SMM) composite was developed by the Centers for Disease Control and Prevention.

2. Please provide a definition of what is considered severe maternal morbidity composite - lines 104-105.

While we agree with the Reviewer that a complete definition of the severe maternal morbidity composite would be ideal in our Introduction, we are limited due to the 250 word maximum for this section. For this reason we expand on the definition of the severe maternal morbidity composite in the Methods section. That being said, we did elaborate on the severe maternal morbidity composite in the Introduction to address this Reviewer comment as well as Reviewer 3, Comment 3 below.

Lines 104-106: In an attempt to understand rare complications that might contribute to maternal mortality, the severe maternal morbidity composite was developed by the Centers for Disease Control and Prevention. This composite includes 21 severe maternal morbidity indicator events, such as eclampsia and cardiac arrest.[11–13]

3. With regards to referencing the CDC SMM Indicators, I would suggest reference 12 is included in the introductory paragraph as that's is where these indicators are explained in details.

We have made the suggested change as shown in Reviewer 3, Comment 2 above.

4. This study is described as an observational cohort. Are cohort studies not by themselves observational? I will suggest dropping the cohort.

We have changed our phrasing for the study design as suggested. Please see response to Reviewer 2, Comment 1. Changes shown below.

Lines 51-52: We retrospectively examined severe maternal morbidity using linked birth certificate and maternal hospital discharge records in California between 2007 and 2012.
Lines 118-120: This was a cohort study of pregnancies in California between 2007 and 2012 to assess risks of maternal epilepsy in pregnancy. Data were analyzed retrospectively.

5. Was this a prospective or retrospective study? This is not clear. The authors should state very clearly what this was - I am guessing it was a retrospective study.

We have incorporated the suggested changes. Please see response to Reviewer 3, Comment 4 above.

6. Presumably SMM was compared between those with epilepsy and the general obstetric population. If this was the case will this be considered a justifiable comparison? If various confounders were taken into analysis then this would be acceptable but if this was not, then possible biased could have been introduced in the analysis.

The Reviewer raises an excellent point about use of the proper referent group. Some have suggested using people with epilepsy not on antiepileptic medications as a referent group. However, this still introduces potential bias due to misclassification of the exposure since most people with active epilepsy will require medication therapy. For this reason, the referent group for our study was the general obstetric population. We did adjust for multiple potential confounders in different statistical models in order to address this issue.

7. Epilepsy was classified as generalized, focal and other types - lines 138-140. Could the other types be given in brackets after the other types for the interest of this reader and presumably others?

The definitions of the ICD-9 CM codes for other types of epilepsy have been added to the Methods section as shown below.

Lines 141-144: Focal or other less specified epilepsy included a composite of focal (345.4, 345.5), localization-related (345.7), and other types (345.2 "petit mal status", 345.3 "grand mal status", 345.8 "other forms of epilepsy and recurrent seizures", 345.9 "epilepsy unspecified").

8. Lines 151-152. Not very clear what 'a patient with generalized epilepsy and epilepsy in complicating pregnancy' mean. It seems as if these are two different conditions. Please clarify or rephrase.

We appreciate the Reviewer's suggestion to clarify this part of our Methods section. These categories were selected based on ICD-9 CM codes (e.g. 345.0 for "generalized nonconvulsive epilepsy" versus 649.4 for "Epilepsy complicating pregnancy, childbirth, or the puerperium". Further description of how epilepsy subgroups were defined has been added to the Methods as shown below (i). In addition, the purpose of the sentence referenced here was to give an example of the hierarchy for how patients were assigned into epilepsy subtypes based on ICD-9 codes. Since the wording was initially confusing, we have rephrased the example as shown below (ii).

(i) Lines 140-148: Generalized epilepsy was identified using ICD-9 CM codes 345.0 and 345.1. Focal or other less specified epilepsy included a composite of focal (345.4, 345.5), localization-related (345.7), and other types (345.2 "petit mal status", 345.3 "grand mal status", 345.8 "other forms of epilepsy and recurrent seizures", 345.9 "epilepsy unspecified"). These types were grouped due to anticipated small numbers limiting our ability to report rare outcomes between them. Two distinct unspecified epilepsy groups were created based on frequently encountered ICD-9 CM codes; code 649.4 was used for unspecified "Epilepsy complicating pregnancy, childbirth, or the puerperium" and code 780.39 was used for "Convulsions".
(ii) Lines 155-157: For example, a patient with ICD-9 CM codes for both generalized epilepsy (e.g. 345.0) and convulsions (780.39) was categorized under the generalized subtype only.

9. In the outcomes the primary one was SMM (line 155) - presumably this is composite SMM rather than just SMM as stated later at line 157. Would it not be useful to add secondary outcomes at line 158 or somewhere in this section?

We have rephrased this section to incorporate the Reviewer's suggestions as shown below.

Lines 159-162: The primary outcome was the severe maternal morbidity composite during the delivery admission or during a subsequent hospital admission up to 42 days postpartum. The severe maternal morbidity composite was defined using the Centers for Disease Control and Prevention indicators and their corresponding ICD-9-CM codes.[13]
Lines 185-187: Secondary outcomes included obstetric complications such as preeclampsia (with and without severe features), gestational diabetes, stillbirth, preterm birth, induction of labor, and cesarean birth.

10. Lines 163-165 - see comment above on comparisons.

The introduction to this sentence has been rephrased to better demonstrate that the evaluation of the SMM indicator events is a continuation of the analysis of SMM.

Lines 169-170: Next, all 21 severe maternal morbidity indicators were individually evaluated and compared between people with and without epilepsy.

11. In the organ system groups there is 'hemorrhage SMM' and 'transfusion SMM'. Presumably these are inter-related?

We agree with the Reviewer that "hemorrhage SMM"(disseminated intravascular coagulation, shock, or hysterectomy) and "transfusion SMM" are likely inter-related in many cases. While it seems reasonable to group these events, the amount of blood transfused is unknown in administrative data. Because of this ambiguity, there are growing efforts to examine non-transfusion SMM.[6,11] *In accordance with this practice, we chose to group "transfusion SMM" in its own category distinct from "hemorrhage SMM". We have clarified this point in the Methods sections.*

Lines 179-182: Transfusion severe maternal morbidity was considered as a separate group from hemorrhage because of the aforementioned ambiguity in administrative data of number of units transfused and the emerging importance of

non-transfusion severe maternal morbidity.

12. In the confounding variables, there is no mention of previous obstetric factors. It is recognized that some of the SMM indicators have a high recurrent or increase the risk of recurrence. Why was this not included in the analyses? It may well be that these data were not available. If that is the case, a comment should be made to this effect.

We agree with the Reviewer that prior obstetric factors can influence the risk of SMM in a subsequent pregnancy. However, by adjusting for the obstetric comorbidity score, we attempted to capture most scenarios that are often associated with recurrent pregnancy risks. We do report some prior obstetric factors, such as prior cesarean, in Table 2. Furthermore, while history of SMM itself may increase the risk of SMM in a subsequent pregnancy, we are not specifically evaluating SMM recurrence and would be wary of including an adjustment for history of the outcome in our models.[14] *That being said, understanding recurrent SMM is an active area of interest for our team.*[15]

13. These are in general well presented. Some of the tables are too busy and it may be better to reduce the variables and emphasize those with significance since he narrative states these are well.

We appreciate this feedback. For simplification, we have edited Table 5 to remove variable rows where odds ratios were not reported. A new footnote has been added to Table 5 to reflect this.

Line 555-561: ‡Odds ratios not reported if models did not converge due to extremely small cell frequencies. Variables not shown because of this are: acute myocardial infarction, aneurysm, and cardiac arrest/ventricular fibrillation for cardiac SMM; temporary tracheostomy and mechanical ventilation for pulmonary SMM; and amniotic fluid embolism for other OB SMM.

14. Figure 2 does not really add much to what is Table 5. Furthermore, when you combined the figures for cardiac and pulmonary SNMM these add to less than what is presented in the Figure. The other variables match those in the Figure.

While the Reviewer is correct that the data shown in Figure 2 are also presented in Table 5, we believe that Figure 2 aids in interpretation of Table 5. In addition, Table 5 allows a granular assessment of our results that is lacking from Figure 2. For these reasons, we would prefer to include both Figure 2 and Table 5 if the Editors are amenable.

We have also checked the numbers, and the combined total of 0.9% for cardiopulmonary events in people with epilepsy versus 0.2% for people without appears correct in the Figure. If the Editors prefer, we can break the combined cardiopulmonary group back out into the individual cardiac and pulmonary groups. These were originally condensed to aid in visual interpretation, and also because we felt it was a clinically relevant combination for descriptive purposes in the Figure.

15. DISCUSSION: This is relevant and deals with the important issues in the study. The very high preterm delivery rate in those with epilepsy compared to the general population highlights the point raised above about appropriate controls. A preterm delivery rate of 41.9% is very high

indeed. Were there any data on the degree of control of the epilepsy and if so were these included in the analyses?

We thank the Reviewer for this feedback. We would like to note that the preterm birth rate in our study was 13.5%; the rate of 41.9% referenced by the Reviewer in this comment is what we found for cesarean birth among people with epilepsy. Unfortunately, we were limited in ascertaining epilepsy control as there is no reliable code for an individual seizure event since clinicians often use the code for the patient's specific epilepsy subtype if they present to the hospital with a seizure. In addition, administrative data are limited in ascertainment of seizure events, especially those that occur out of the hospital. We attempted to address this limitation by examining the epilepsy subtypes. We expand on the possible role that antiseizure medications might play in pregnancy outcomes in our Discussion section as well. We agree that further investigation into how disease control affects pregnancy outcomes is warranted, and hope our manuscript might help inspire such research. We have clarified this in our limitations section.

Lines 355-357: There likely remain unmeasured confounders which were not accounted for or were not included due to concerns about coding reliability (e.g. smoking status, cesarean indication, or epilepsy disease control).

16. While there are comments on the strengths of the study, no attempt is made to highlight the limitations. I would like to see some of these especially if the data were collected retrospectively.

We agree with the Reviewer that our study has limitations. Our limitations paragraph was presented after our study strengths in Line 322 of the original manuscript. We have rephrased the beginning of this paragraph to clarify that this was intended as the limitations section. The entire revised paragraph is shown below.

Lines 352-361: Our results must be interpreted within the context of the study design and limitations. Though timing of events was not available retrospectively, we attempted to address causality between epilepsy and severe maternal morbidity by restricting only to epilepsy codes present on admission. There likely remain unmeasured confounders which were not accounted for or were not included due to concerns about coding reliability (e.g. smoking status, cesarean indication, or epilepsy disease control). Due to data use agreements, we are unable to report rates of very rare outcomes such as maternal mortality. Though our results may not be generalizable to populations outside of California, California is diverse and accounts for the greatest total number of births in the United States.[16]

17. References: These are up-to-date although do not conform to the style for the Journal.

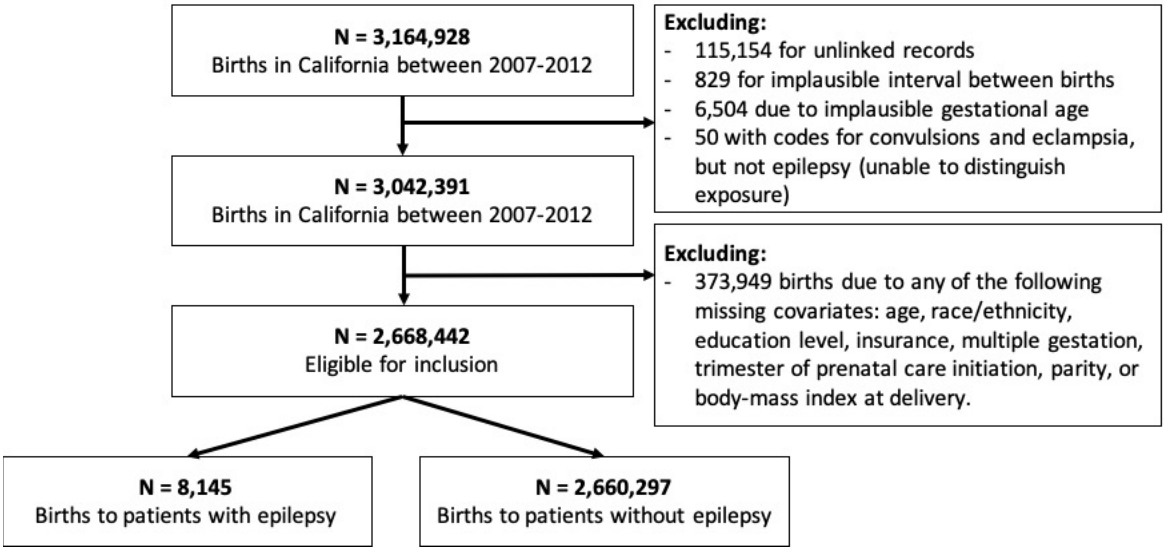
We have reviewed and updated the References to conform to the style of the Green Journal. Please let us know if additional edits are needed for specific references.

STATISTICAL EDITOR COMMENTS:

1. Lines 128-130: Of all births in California during the years of this study, how many N(%) were not linked or otherwise excluded?

We have added a line to Figure 1 showing that 115,154 records were unlinked and therefore excluded.

Figure 1:



2. Lines 211-213, 267-269, & Supplementary Table: Need to include in supplemental material the results of the matching process, including the N from each group after the match, the closeness of the match for all the relevant variables and replication of Table 3, to compare with its output based on multivariable adjustment. Suggest including in main text, if possible.

We have included the requested information in 3 new appendices. Appendix 1 is the model output (uploaded as a supplement), and Appendix 2 and 3 (uploaded in same supplement and shown below) are replications of Tables 3 and 4 using propensity matching. If the Editors prefer these be included in the main text, we are happy to do so.

***Appendix 2**. Propensity score matched results for adjusted risk of severe maternal morbidity among patients with epilepsy compared to patients without epilepsy in California, 2007-2012.*

Exposure group	N (row %)	Model 1 Crude OR (95% CI)	Model 2* Adjusted OR (95% CI)	Model 3† Adjusted OR (95% CI)
Patients without epilepsy (N=8,145)	109 (1.3)	Reference	Reference	Reference
All patients with epilepsy‡ (N=8,145)	350 (4.3)	3.10 (2.79-3.45)	3.31 (2.66-4.11)	2.07 (1.72-2.49)
Generalized epilepsy (N=637)	49 (7.7)	5.76 (4.30-7.71)	6.14 (4.34-8.70)	3.84 (2.77-5.33)
Focal epilepsy and other less specified epilepsies (N=6,250)	241 (3.9)	2.77 (2.44-3.15)	2.96 (2.35-3.72)	1.85 (1.52-2.25)
Unspecified epilepsy complicating pregnancy, childbirth, or the puerperium	14 (4.9)	3.58 (2.09-6.13)	3.82 (2.16-6.76)	2.39 (1.37-4.17)

(N=284)				
Convulsions only (N=974)	46 (4.7)	3.43 (2.55-4.61)	3.65 (2.57-5.19)	2.28 (1.64-3.18)

[*]Model 2 matched on maternal age, race or ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity.
[†] Model 3 additionally match on validated obstetric comorbidity score. See text for details.
[‡]Refer to text for details regarding categorization of epilepsy subtypes.

***Appendix 3**. Propensity score matched results for adjusted risk of non-transfusion severe maternal morbidity among patients with epilepsy compared to patients without epilepsy in California, 2007-2012.*

Exposure group	**N (row %)**	**Model 1 Crude OR (95% CI)**	**Model 2[*] Adjusted OR (95% CI)**	**Model 3[†] Adjusted OR (95% CI)**
Patients without epilepsy (N=8,145)	72 (0.9)	Reference	Reference	Reference
All patients with epilepsy[‡] (N=8,145)	234 (2.9)	3.10 (2.79-3.45)	3.32 (2.54-4.33)	2.65 (2.07-3.38)
Generalized epilepsy (N=637)	38 (6.0)	5.76 (4.30-7.71)	7.11 (4.76-10.63)	5.68 (3.85-8.37)
Focal epilepsy and other less specified epilepsies (N=6,250)	162 (2.6)	2.77 (2.44-3.15)	2.98 (2.26-3.95)	2.38 (1.84-3.09)
Unspecified epilepsy complicating pregnancy, childbirth, or the puerperium (N=284)	<15	3.58 (2.09-6.13)	2.42 (1.04-5.61)	1.93 (0.84-4.45)
Convulsions only (N=974)	28 (2.9)	3.43 (2.55-4.61)	3.32 (2.13-5.16)	2.65 (1.72-4.07)

Sample size <15 not shown per data use agreement.
[*]Model 2 matched on maternal age, race or ethnicity as a social determinant, method of payment, education level, trimester of prenatal care initiation, and parity.
[†] Model 3 additionally match on validated obstetric comorbidity score. See text for details.
[‡]Refer to text for details regarding categorization of epilepsy subtypes.

3. Table 1: Need units for BMI.

BMI units have been added.

4. Lines 332-333: To put the increased risk in context, how would epilepsy as a risk factor for SMM (both in absolute and relative terms), compare with other known risk factors for SMM? Might be useful as another Table, even though it may not be modifiable.

We would like to thank the statistical Editor for this excellent suggestion. We have added this to our Discussion section.

Lines 308-310: To put our results into context, the risk of SMM with epilepsy was higher than what has been demonstrated with other conditions such as autoimmune disease (aRR 1.80, 95% CI 1.73-1.87).[6]

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

OPT-IN: Yes, please publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page. The following authors need to complete the form:
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The authors have verified their authorship.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor. If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

We have confirmed that the transparency declaration statement is included in our cover letter.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

We have clarified in the Methods section that our data for race or ethnicity were obtained from the birth certificate, where it is self-reported by patients. We also discuss in the manuscript that race or ethnicity data were assessed in our study as social constructs given prior evidence of association between socioeconomic status and adverse pregnancy outcomes.

Lines 193-195: Race or ethnicity were obtained from the birth certificate, where it is self-reported by the patient. This approach has been previously validated using California birth certificate data.[8]

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

The STROBE checklist has been uploaded with this revision.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

To the best of our ability, the reVITALize definitions have been utilized in this manuscript. If the Editors identify additional terms that we missed we are happy to convert them to adhere to reVITALize definitions.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

Our revised manuscript is under 5,500 words.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:
* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or Editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Due to the COVID-19 pandemic, the authors decided to proceed directly with manuscript submission for this study rather than delaying in order to enable presentation at a scientific meeting. The acknowledgements and funding sections are updated and accurate.

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

The short title for this manuscript is "Severe maternal morbidity with epilepsy".

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully. In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

The authors confirm that the abstract should be correct and adhere to journal guidelines. The Abstract word count is 296. This has been added to the title page.

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript. Please spell out "SMM" throughout your manuscript, except in tables and figures.

We have replaced SMM throughout the manuscript with "severe maternal morbidity". Given constraints of the Abstract word count, replacing "SMM" with "severe maternal morbidity" would put the Abstract well beyond the 300 word limit. The authors feel that cutting components of the Abstract to accommodate this change detracts from the findings of our study. If the Editors are amenable, we would prefer to keep the "SMM" designation for the Abstract if possible. For similar reasons, we would also prefer to keep "SMM" in the tables if the Editors are amenable.

12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

This symbol has been removed where appropriate.

13. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

"Provider" has been changed to "physician" in line 318.

14. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts. Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

We present effect sizes as odds ratios where applicable in our results. Due to our study design, we do not feel that reporting a number needed to harm or treat would be appropriate. Lastly, our p-values are standardized to two decimal places if ≥ 0.01 and three decimal places if <0.01. Percentages are listed to one decimal place.

15. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

The tables should confirm to journal style. If the Editors note specific areas where this was missed we are happy to revise.

16. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list. In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

We have updated our references to reflect the journal style.

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The corresponding author will await receipt of this email.

Response to Review References

1. French JA, Kanner AM, Bautista J, et al. Practice Parameters, Efficacy, and Tolerability of the New Antiepileptic Drugs: Treatment of New-Onset Epilepsy. Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. *Epilepsia*. 2004;45(5):401-409.
2. Centers for Disease Control and Prevention. More Americans have epilepsy than ever before. Published 2017. Accessed February 25, 2019. https://www.cdc.gov/media/releases/2017/p0810-epilepsy-prevalence.html
3. Hessler A, Dolbec K. Clinical updates in women's healthcare: Seizures. *Am Coll Obstet Gynecol*. 2021;XX(I).
4. MacDonald SC, Bateman BT, McElrath TF, Hernández-Díaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States.

JAMA Neurol. 2015;72(9):981-988. doi:10.1001/jamaneurol.2015.1017
5. Ho DE, King G, Stuart EA, Imai K. MatchIt : Nonparametric Preprocessing for. *J Stat Softw*. 2011;42(8):1-28. http://www.jstatsoft.org/v42/i08/paper
6. Leonard SA, Kennedy CJ, Carmichael SL, Lyell DJ, Main EK. An Expanded Obstetric Comorbidity Scoring System for Predicting Severe Maternal Morbidity. *Obstet Gynecol*. 2020;136(3):440-449. doi:10.1097/AOG.0000000000004022
7. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association between pregnancy and perinatal outcomes among Women with epilepsy. *JAMA Neurol*. 2017;74(8):983-991. doi:10.1001/jamaneurol.2017.1310
8. Baumeister L, Marchi K, Pearl M, Williams R, Braveman P. The validity of information on "race" and "Hispanic ethnicity" in California birth certificate data. *Health Serv Res*. 2000;35(4):869-883. http://www.ncbi.nlm.nih.gov/pubmed/11055453%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1089157
9. Leach J, Smith P, Craig J, et al. Epilepsy and Pregnancy: For healthy pregnancies and happy outcomes. Suggestions for service improvements from the Multispecialty UK Epilepsy Mortality Group. *Seizure*. 2017;50(2017):67-72. doi:10.1016/j.seizure.2017.05.004
10. Rosenstein MG, Chang SC, Sakowski C, et al. Hospital Quality Improvement Interventions, Statewide Policy Initiatives, and Rates of Cesarean Delivery for Nulliparous, Term, Singleton, Vertex Births in California. *JAMA - J Am Med Assoc*. 2021;325(16):1631-1639. doi:10.1001/jama.2021.3816
11. Main EK, Abreo A, McNulty J, et al. Measuring severe maternal morbidity: Validation of potential measures. *Am J Obstet Gynecol*. 2016;214(5):643.e1-643.e10. http://dx.doi.org/10.1016/j.ajog.2015.11.004
12. Main EK. Reducing Maternal Mortality and Severe Maternal Morbidity Through State-based Quality Improvement Initiatives. *Clin Obstet Gynecol*. 2018;61(2):319-331. doi:10.1097/GRF.0000000000000361
13. Centers for Disease Control and Prevention. Severe Maternal Morbidity Indicators and Corresponding ICD Codes during Delivery Hospitalizations. Accessed March 11, 2019. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm
14. Howards PP, Schisterman EF, Poole C, Kaufman JS, Weinberg CR. "Toward a clearer definition of confounding" revisited with directed acyclic graphs. *Am J Epidemiol*. 2012;176(6):506-511. doi:10.1093/aje/kws127
15. Bane S, Wall-Wieler E, Lyndon A, Carmichael SL. Recurrence of severe maternal morbidity: A population-based cohort analysis of California women. *Paediatr Perinat Epidemiol*. 2021;35(2):155-161. doi:10.1111/ppe.12714
16. Martin J, Hamilton B, Osterman M, Driscoll A. Births: Final Data for 2019. *Natl Vital Stat Reports*. 2021;70(2):1-51.