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)*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

Date: Apr 02, 2021
To: "Marleen van Gelder"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-85

RE: Manuscript Number ONG-21-85

Associations between maternal depression, use of antidepressants during pregnancy, and adverse pregnancy outcomes: an individual participant data meta-analysis

Dear Dr. van Gelder:

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).

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 Apr 23, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Overall: This is an individual patient meta analysis of the association between maternal depression, antidepressant use in pregnancy, and adverse pregnancy outcomes (specifically, preterm birth, low birthweight, small-for-gestational age birthweight, and low Apgar scores). This study adds power by combining many smaller studies, and adds evidence to a question that is both clinically relevant and difficult to study using randomized controlled trials. Overall as this question is still far from settled I think this paper adds information that will be clinically useful when counseling patients about antidepressant use in pregnancy. I did get very confused, when reading the methods and results section, what groups of women all of the different 'cohorts' were meant to contain, and would suggest the authors stick to one or two comparison groups rather than 4 (more?).
Specific comments are as follows:
Introduction:
1. Lines 121-122: How would we define 'moderate to severe' depression?
2. Nice justification for why this study adds something above and beyond other reviews and meta-analyses.

Methods:
1. Lines 225-30: Is it true that you have a cohort of women for whom they are taking antidepressants, but without symptoms of depression or a diagnosis of depression? Who are these women and why are they taking these medications? (anxiety disorders? Neuropsychiatric pain?) While I can see that it is tempting to use these women as a 'control' for the effect of antidepressants in the absence of depression, they must be taking these medications for some other reason and thus there would remain the potential for confounding by indication.

2. Did you consider using propensity scores to control for whether there were differences between women who were treated with antidepressants vs. those who were not?

Results:
1. A flowchart describing your different cohorts would be helpful (in addition to the flowchart you already have).
2. Lines 290-1: can you put in the p values for comparisons?
3. Lines 297-8: I am confused about how women in the depression cohort did not have a diagnosis of depression.

Discussion:
1. Your discussion of study limitations is good, but I do wonder if you still have residual confounding from treatment bias of women with depression - many other studies have adjusted for this using propensity score analysis to control for likelihood

of treatment. This may have been too much for this study but I want you to acknowledge this drawback more than you have already.

Reviewer #2:

This is a systematic review and individual patient data meta-analysis (MA) that examines associations between depression and use of antidepressants during pregnancy with preterm birth, SGA, low birth weight, and low Apgar score. One-step random effects approach was used to conduct the study of 402,375 women included in 27 databases. The authors conducted the analysis in 4 study cohorts: full depression cohort, depression cohort restricted to women without antidepressant use, antidepressant cohort, and antidepressant cohort restricted to women with depressive symptoms or clinical diagnosis of depression. They concluded that clinical diagnosis of depression and/or depressive symptoms are associated with preterm birth and low Apgar scores, even without the use of antidepressants. The use of selective serotonin inhibitors was also associated with these outcomes.
The following questions and comments to address:
- All included studies were observational in design, what was the reason to use PRISMA guidelines instead of MOOSE guidelines?
- Did you attempt to locate unpublished databases to examine whether published bias exists?
- It is important to report the design of the studies included for the MA, the number of participants analyzed in the MA, and the difference of the sample size for each study in the MA respecting to the sample size analyzed in the original studies.
- In appendix 2, add the year of publication of the studies included in the MA.
- Women with depression diagnosis, depressive symptoms and anxiety are included in multiple studies. The authors did not describe whether women with diagnosis of anxiety were excluded at all from the analysis or if they were analyzed in any of the selected cohorts. This needs clarification.
- Does the definition of low birth weight < 2500 grams apply only for term deliveries? It would be better to analyze birth weight as a continuous variable and to establish birth weight mean differences between the exposed and unexposed cohorts.
- Although the authors control for multiple confounders, conditions related to poor fetal growth, preterm delivery, and low Apgar scores such as hypertensive disorders of pregnancy, fetal growth restriction, and intrapartum factors were not taken into account. This limitation needs to be acknowledged.
- Analyses should be control for the concomitant use of other psychotropic medications such as anti-anxiety and antipsychotic medications
- Clarify whether the preterm delivery outcome includes spontaneous, indicated, or a combination of both. Can you conduct an analysis on early and late preterm delivery subgroups?
- Lines 238-239, the authors state "statistical heterogeneity was taken into account." Which statistical method was used to test heterogeneity?
- Lines 287-294, this paragraph is very confusing. A better way is to describe how the absolute risks for the respective outcomes change from the absence to the presence of depressive symptoms or clinical diagnosis, depressive symptoms, and clinical diagnosis for the full cohort and for the restricted cohort restricted to women without antidepressant use.
- Data on the use of concomitant use of multiple antidepressant medications by individual patients need to be reported and analyzed.
- Avoid using "and/or" throughout the article, simply use or.
- Although the authors acknowledge the data do not allow to determine when in gestation the antidepressant medications were started or whether they are suspended an any time and further analysis on medication dose could not be accomplished. They also need to acknowledge, the data are limited by the inconsistencies regarding the timing in pregnancy when assessment of depression or depressive symptoms was performed across the individual studies. For instance, diagnosis of depression or presence of depressive symptoms in the third trimester reported in a particular study cannot determine whether the diagnosis or symptoms were present at earlier gestational ages.
- The authors need to grade the quality of the analyzed data and based on the assessment make, if any, clinical practice recommendations.

Reviewer #3:

Vlenteri et al performed an individual participant data meta-analysis on maternal depression and use of antidepressants and adverse perinatal outcomes in pregnant women.
Abstract:

95 Why did authors choose to not search beyond June 2016?
Conclusions are appropriate for this manuscript.

Introduction: Good

Materials and Methods:
Study was registered with PROSPERO.
165-168 Sources appears appropriate and complete.
172-173, 177-180 Data abstraction was performed by 2 reviewers; disagreements were settled by a third person.
Translation was used for non-English manuscripts.
173-175 Explicit criteria for study selection is clear.
175-177 Exclusion criteria were clear.
214-215 dichotomously "to"
217-220 Did the authors explore 1st and number of prenatal visits, marital status and history of preterm birth or SGA as confounders? Why did the authors choose epilepsy and folic acid as a potential confounding variables?
PRISMA guidelines provided.

Results:
300-302, 314-326, 319-320, 327-328 aORs include 1.0 and should not be interpreted as significant.
Recommend authors discuss role of heterogeneity in the cautious interpretation of their results.

Discussion:
390-420 Appreciate the authors thorough discussion of limitations.
446-449 Associations between SSRI use and preterm birth and low 5 minute APGAR in restricted group is no longer significant as CI includes 1.0.

Conclusion:
455-460 Given the heterogeneity of studies in this meta-analysis and wide CIs found in some of their results, suggest that the authors recommend further comparative research for this controversial topic; would suggest deleting "carefully selecting the type of antidepressant prescribed", especially as evaluation of SSRIs was done as a secondary outcome.

Figures and Tables: Figure 1. Sp "Asses" to "Assess"

References: Appropriate for study.

STATISTICS EDITOR COMMENTS:

General and Table 1: This is a large cohort of IPD level data and all subsets have large sample sizes.

Table 2: However, the risks and associations are either NS or the strength of association is quite modest. The statistical associations are largely due to the large sample sizes and there is no adjustment for multiple hypothesis testing, which would make some of the associations NS. The differences between cohorts with depression but with vs without antidepressant use are in some cases statistically significant, albeit again modest in degree. Since the samples are mostly quite large, the Authors should corroborate their analyses with a matching algorithm, in addition to the multivariable logistic method.

Table 3: Same issues as in Table 2 regarding mostly modest associations, no adjustment for multiple hypothesis testing and need to corroborate with matching approach.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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:

A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.

3. 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.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. 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.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. 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]."

7. 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 Reviews is 300 words. Please provide a word count.

8. 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.

9. 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.

10. ACOG is moving toward discontinuing the use of "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.

11. 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%").

12. 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 reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page

at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

13. Figure 1: Please check the n values in the second exclusion box to make sure they total to 202.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

14. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

* 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 Apr 23, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD
Editor-in-Chief

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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Dear Dr. Rouse,

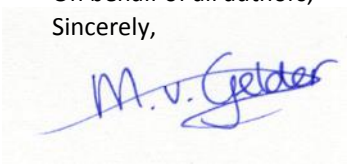
Enclosed please find the revised manuscript entitled 'Associations between maternal depression, use of antidepressants during pregnancy, and adverse pregnancy outcomes: an individual participant data meta-analysis' (ONG-21-85), that I would like to resubmit for publication in Obstetrics & Gynecology. In this revised manuscript, we have taken the Reviewer comments, Statistics Editor comments, and Editorial Office comments into account. The changes made are described below in detail.

The paper has not previously been published, either in whole or in part, and no similar paper is in press or under review elsewhere. All authors were personally and actively involved in substantive work leading to this paper and hold themselves jointly and individually responsible for its content. All authors have approved the resubmission of the final manuscript.

The senior author(dr. Nel Roeleveld) 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 have been explained.

We hope that you would be so kind as to consider this revised manuscript for publication in Obstetrics & Gynecology.

On behalf of all authors,
Sincerely,



M.M.H.J. van Gelder, PhD

REVIEWER COMMENTS:

Reviewer #1:

Overall: This is an individual patient meta analysis of the association between maternal depression, antidepressant use in pregnancy, and adverse pregnancy outcomes (specifically, preterm birth, low birthweight, small-for-gestational age birthweight, and low Apgar scores). This study adds power by combining many smaller studies, and adds evidence to a question that is both clinically relevant and difficult to study using randomized controlled trials. Overall as this question is still far from settled I think this paper adds information that will be clinically useful when counseling patients about antidepressant use in pregnancy. I did get very confused, when reading the methods and results section, what groups of women all of the different 'cohorts' were meant to contain, and would suggest the authors stick to one or two comparison groups rather than 4 (more?).
Response: We do not think eliminating comparison groups would be a good approach, as the additional sub-groups in Tables 2 and 3 account for confounding by indication. We would lose a lot of data and decrease the clinical relevance of this study if we did. To further explain the different comparison groups, we added a detailed explanation of the cohorts below. We also incorporated some of these details in the revised description of the cohorts in the methods section (lines 237 – 246) and tried to clarify the result by adding the name of the specific cohort here and there in the results section (e.g. lines 286 – 287, 289, 298, 302, 340, and 354). If you feel that we need to add any additional information, we would be happy to oblige.

Cohort 1 – Depression cohort: All women with information present on depressive symptoms or a clinical diagnosis of depression. These include women without symptoms, with symptoms, without a diagnoses, and with a diagnosis.
Cohort 2 – Depression cohort restricted to women without antidepressant use: All women with information present on depressive symptoms or a clinical diagnosis of depression (group 1), but excluding women who used antidepressants during pregnancy and those for whom no information was available about antidepressant use during pregnancy.
Cohort 3 – Cohort antidepressant use: All women with information present on antidepressant use. These include women without antidepressant use and women with antidepressant use.
Cohort 4 – Cohort antidepressant use restricted to women with depressive symptoms or clinical diagnosis of depression: All women with information present on antidepressant use (group 3), but excluding women without depressive symptoms or a clinical diagnosis of depression.

Specific comments are as follows:

Introduction:

1. Lines 121-122: How would we define 'moderate to severe' depression?
Response: According to the DSM IV, moderate to severe depression is defined by different criteria than minor depression, including more depressive symptoms which occur over a longer period of time. In this study, we did not perform sub-analyses on minor vs moderate/severe depression as this information was often lacking from the studies included.

2. Nice justification for why this study adds something above and beyond other reviews and meta-analyses.
Response: Thank you. We agree that this study can definitely add important and crucial information to the existing body of literature on this topic. To emphasize that this is not just a single study, we changed ‘this study’ into ‘this meta-analysis’ or ‘this IPD meta-analysis’ where appropriate throughout the manuscript.

Methods:
1. Lines 225-30: Is it true that you have a cohort of women for whom they are taking antidepressants, but without symptoms of depression or a diagnosis of depression? Who are these women and why are they taking these medications? (anxiety disorders? Neuropsychiatric pain?) While I can see that it is tempting to use these women as a 'control' for the effect of antidepressants in the absence of depression, they must be taking these medications for some other reason and thus there would remain the potential for confounding by indication.
Response: Indeed, antidepressants are sometimes prescribed for other indications, such as anxiety disorders or neuropsychiatric pain. As it happens, no women in our cohort used antidepressants for non-depression indications. This can be seen in Tables 1 and 3, where the numbers of women using antidepressants in the *Cohort antidepressant use* are exactly the same as those in the *Cohort antidepressant use restricted to women with depressive symptoms or clinical diagnosis of depression*. In the analyses of the former cohort, women with antidepressant use were compared to all women without antidepressant use in the studies included, without taking the indication into account. To address confounding by indication, the analyses in the latter cohort only included women who used antidepressant for the indication depression compared to women with depressive symptoms or a clinical diagnosis of depression but without using antidepressants.

2. Did you consider using propensity scores to control for whether there were differences between women who were treated with antidepressants vs. those who were not?
Response: We did consider the use of propensity scores in the individual participant data meta-analyses, but after consulting with a statistician with expertise in IPD meta-analyses, we decided not to use this statistical method. Using propensity scores is especially advantages in situations with small numbers and many potential confounders (incl. confounding by indication), which was not the case in our meta-analysis. In addition, we used a different initial confounder set for each outcome. Therefore, the best approach was in our view to use one-stage random-effects meta-analyses.

Results:
1. A flowchart describing your different cohorts would be helpful (in addition to the flowchart you already have).
Response: We added a graphical explanation of the different cohorts in Figure 2, but would of course be willing to supply a flowchart if preferred.

2. Lines 290-1: can you put in the p values for comparisons?
Response: The numbers here are purely descriptive to give an impression of the magnitudes of the different outcomes. The comparisons are represented by odds ratios with 95% confidence intervals (in Tables 2 and 3 and in the description in the text underneath the indicated lines) according to the guidelines of the journal. These provide more information for interpretation than p values.

3. Lines 297-8: I am confused about how women in the depression cohort did not have a diagnosis of depression.
Response: The depression cohort contains all women with data available on 'depressive symptoms or a clinical diagnosis of depression'. This means that some women had a clinical diagnoses of depression issued by a health care professional, whereas other women had depressive symptoms assessed by the use of validated self-reported questionnaires (e.g. the Edinburgh Postpartum Depression Scale / Edinburgh Depression Scale (EPDS / EDS) and the Primary Care Evaluation of Mental Disorders Patient Questionnaire (PRIME-MD), which is quite common in observational studies. But the vast majority of women had neither a diagnosis of depression nor depressive symptoms. See Appendix 2 for information on the different methods

of data collection and which studies assessed a clinical diagnosis of depression and which studies assessed depressive symptoms.

Discussion:
1. Your discussion of study limitations is good, but I do wonder if you still have residual confounding from treatment bias of women with depression - many other studies have adjusted for this using propensity score analysis to control for likelihood of treatment. This may have been too much for this study but I want you to acknowledge this drawback more than you have already.

Response: We agree that it will never be possible to completely rule out the possibility of treatment bias in women with depression. However, propensity score adjustment does not completely fix this bias either. By also performing the analyses within the restricted antidepressant use cohort in Table 3, we tried to account for treatment bias by excluding all women who did not have a diagnosis of depression or depressive symptoms and could therefore not have been treated for the indication depression. Still, women with less severe depression may not have been treated pharmacologically in the same amount as women with severe depression, so some treatment bias (confounding by severity) may still have occurred. A comment to this effect was added to the limitation section in the discussion.

Discussion lines 451 - 455:

To minimize treatment bias, we also performed the analyses within the restricted antidepressant use cohort excluding all women who did not have a diagnosis of depression or depressive symptoms and could therefore not have been treated for depression. Still, women with less severe depression may not have been treated pharmacologically in the same amount as women with severe depression, so some treatment bias may still have occurred.

Reviewer #2:

This is a systematic review and individual patient data meta-analysis (MA) that examines associations between depression and use of antidepressants during pregnancy with preterm birth, SGA, low birth weight, and low Apgar score. One-step random effects approach was used to conduct the study of 402,375 women included in 27 databases. The authors conducted the analysis in 4 study cohorts: full depression cohort, depression cohort restricted to women without antidepressant use, antidepressant cohort, and antidepressant cohort restricted to women with depressive symptoms or clinical diagnosis of depression. They concluded that clinical diagnosis of depression and/or depressive symptoms are associated with preterm birth and low Apgar scores, even without the use of antidepressants. The use of selective serotonin inhibitors was also associated with these outcomes.
The following questions and comments to address:

- All included studies were observational in design, what was the reason to use PRISMA guidelines instead of MOOSE guidelines?

Response: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines is an evidence-based minimum set of items which is well-known and is commonly used in the setup of IPD meta-analyses. The MOOSE guidelines contain specifications for reporting of meta-analyses of observational studies, which could also have been used for this study. As PRISMA guidelines were more commonly used among IPD meta-analyses, we decided to use the latter.

- Did you attempt to locate unpublished databases to examine whether published bias exists?

Response: Because no registry of observational studies exists that is comparable to the registries for Randomized Controlled Trials, it is very difficult, if not impossible, to get a complete overview of unpublished databases. We felt that approaching a selection of unpublished databases that may contain information on the associations of interest would have increased the risk of selection. Therefore, we decided to use databases based on published articles only. We added a statement to this effect to lines 397-398 in the discussion section. We also examined the risk of participation bias within the study by performing a 'traditional' meta-analysis on the included databases from which we could conclude that participation bias was limited (see discussion, lines 404 - 414).

- It is important to report the design of the studies included for the MA, the number of participants analyzed in the MA, and the difference of the sample size for each study in the MA respecting to the sample size analyzed in the original studies.

Response: We fully agree with the reviewer and refer to Appendix 3 in which almost all information the reviewer is requesting is present. By looking at Appendix 3 critically, we discovered that we uploaded an old version with a few errors before. These errors were corrected in the revised version.

- In appendix 2, add the year of publication of the studies included in the MA.

Response: This information is present in the first column of Appendix 2 and Appendix 3.

- Women with depression diagnosis, depressive symptoms and anxiety are included in multiple studies. The authors did not describe whether women with diagnosis of anxiety were excluded at all from the analysis or if they were analyzed in any of the selected cohorts. This needs clarification.

Response: Women with only information present on anxiety symptoms and not on depressive symptoms were automatically excluded from the analyses as only women with data on depressive symptoms (yes/no symptoms) or a clinical diagnosis were included. However, it is possible that women with anxiety symptoms were included in the *Depression cohort* when they also had data available on the presence or absence of depressive symptoms or a clinical diagnosis. A comment about this issue was added to the limitation section in the discussion.

Discussion lines 428 - 431:

These questionnaires often assess symptoms of depression as well as anxiety, so the depression cohort may include many women with symptoms of anxiety alongside depressive symptoms. However, women with only anxiety without depression were excluded from the analyses.

- Does the definition of low birth weight < 2500 grams apply only for term deliveries? It would be better to analyze birth weight as a continuous variable and to establish birth weight mean differences between the exposed and unexposed cohorts.

Response: We decided to analyse the outcome measure birth weight as a dichotomous variable, as this is clinically considered more relevant than a shift in mean birth weight, and because we would otherwise lose a lot of data from databases who only reported this outcome measure in a categorical way. Low birth weight did not only apply to term deliveries, so the preterm birth and low birth weight groups are not mutually exclusive. A footnote to this effect was added to Tables 2 and 3 and to Appendixes 4, 5, and 6.

Footnote to Tables 2, 3 and Appendixes 4, 5, and 6:

Preterm births were not excluded from the low birth weight cases, so these two groups are not mutually exclusive.

- Although the authors control for multiple confounders, conditions related to poor fetal growth, preterm delivery, and low Apgar scores such as hypertensive disorders of pregnancy, fetal growth restriction, and intrapartum factors were not taken into account. This limitation needs to be acknowledged.

Response: Residual confounding can never be ruled out in observational studies and we agree with the reviewer that this also applies to this IPD meta-analysis, as not all databases contained information on all important potentially confounding factors. Some of this information was added to the discussion, but most factors suggested by the reviewer cannot be considered a confounder: foetal growth restriction is most likely an intermediate and intrapartum factors could never cause depression during pregnancy due to timing.

Discussion lines 397 - 401:

Residual confounding may still influence our results, as we did not have any information on pregnancy-related risk factors for the outcomes, such as thyroid problems and hypertensive disorders, or on concomitant use of psychotropic medication other than antidepressants, such as anxiolytics and antipsychotic medication.

- Analyses should be control for the concomitant use of other psychotropic medications such as anti-anxiety and antipsychotic medications

Response: This information was not present in the databases received to perform this IPD meta-analysis. The use of antidepressants was already limited in this study population of pregnant women, and we expect the use of other psychotropic medications to be even less common in a pregnant population. More specific information should be collected in large cohort studies to report and analyse the concomitant use of anti-anxiety and antipsychotic medications. We added these to the statement on residual confounding above (lines 400 – 401).

- Clarify whether the preterm delivery outcome includes spontaneous, indicated, or a combination of both. Can you conduct an analysis on early and late preterm delivery subgroups?

Response: We do not have information on whether the preterm deliveries were spontaneous, indicated, or a combination of both. This type of information is often not present in observational cohort studies. Timing of preterm birth is available in more studies, but adding additional analyses on early and late preterm delivery would probably not provide any new insight. As this manuscript already contains a lot of analyses and sub-analyses, we decided not to perform any additional sub-analyses on preterm delivery. If these sub-analyses would be of interest and we have enough data on timing of delivery, we can consider including this topic in a next study.

- Lines 238-239, the authors state "statistical heterogeneity was taken into account." Which statistical method was used to test heterogeneity?

Response: In one-stage random-effects logistic regression analyses, clustering within studies and statistical heterogeneity are taken into account. That is the reason we chose for this statistical method.

- Lines 287-294, this paragraph is very confusing. A better way is to describe how the absolute risks for the respective outcomes change from the absence to the presence of depressive symptoms or clinical diagnosis, depressive symptoms, and clinical diagnosis for the full cohort and for the restricted cohort restricted to women without antidepressant use.

Response: We agree with the reviewer that the paragraph might be confusing. So we deleted some information to make the paragraph more readable and purely descriptive, just to give an impression of the magnitudes of the different outcomes. We already presented the absolute risks per pregnancy outcome of the women without depressive symptoms or a clinical diagnosis, followed by the (higher) absolute risks for women with these symptoms or a diagnosis in the depression cohort. We now deleted the information on other absolute risks in the last three lines and just stated that these varied (lines 311 – 312). All absolute risks can be found in Tables 2 and 3 for review.

- Data on the use of concomitant use of multiple antidepressant medications by individual patients need to be reported and analyzed.

Response: See also our answer to a previous comment made by the reviewer about the use of other psychotropic medications. Information on multiple use of antidepressants was not present in the databases received to perform this IPD meta-analysis. The use of individual antidepressants was already limited, which would suggest the use of multiple antidepressant by individual patients to be even more scarce. More specific information should be collected in large cohort studies to report and analyse the concomitant or consecutive use of multiple antidepressant medications by individual patients.

- Avoid using "and/or" throughout the article, simply use or.

Response: The words ‘and/or’ were replaced by ‘or’ throughout the manuscript.

- Although the authors acknowledge the data do not allow to determine when in gestation the antidepressant medications were started or whether they are suspended an any time and further analysis on medication dose could not be accomplished. They also need to acknowledge, the data are limited by the inconsistencies regarding the timing in pregnancy when assessment of depression or depressive symptoms was performed across the individual studies. For instance, diagnosis of depression or presence of depressive symptoms in the third trimester reported in a particular study cannot determine whether the diagnosis or symptoms were present at earlier gestational ages.

Response: We fully agree with the reviewer on this point and added a sentence to the discussion.

Discussion lines 421 - 422:
…, measures, as well as on the timing of the assessment of depressive symptoms or a clinical diagnosis of depression.

- The authors need to grade the quality of the analyzed data and based on the assessment make, if any, clinical practice recommendations.
Response: In IPD meta-analyses, it is unusual to use quality grading tools as these grade the quality of separate studies, whereas you combine the individual participant data of multiple studies in an IPD meta-analysis and generate new effect estimates. Therefore, several quality criteria, e.g. pertaining to research question, sample size, selection of cases and controls, and adjustment for confounding in the original studies do not apply. In the discussion section, however, we discuss the limitations of this meta-analysis extensively (lines 385 – 457) and provided a paragraph about the clinical implications of the meta-analysis in light of the results (lines 477 – 489). Please let us know if more information is required.

Reviewer #3:

Vlenteri et al performed an individual participant data meta-analysis on maternal depression and use of antidepressants and adverse perinatal outcomes in pregnant women.
Abstract:

95 Why did authors choose to not search beyond June 2016?
Response: As the work associated with constructing this IPD meta-analysis, performing the systematic literature review, contacting all authors, acquiring adequate databases, performing the meta-analyses, and reporting all results takes a lot of effort, we could not continue adding new literature published after June 2016.

Conclusions are appropriate for this manuscript.
Response: Thank you

Introduction: Good
Response: Thank you

Materials and Methods:
Study was registered with PROSPERO.
165-168 Sources appears appropriate and complete.
Response: Thank you

172-173, 177-180 Data abstraction was performed by 2 reviewers; disagreements were settled by a third person. Translation was used for non-English manuscripts.
Response: Correct

173-175 Explicit criteria for study selection is clear.
Response: Thank you

175-177 Exclusion criteria were clear.
Response: Thank you

214-215 dichotomously "to"

Response: We believe the sentence to be correct as is, so did not add 'to'.

217-220 Did the authors explore 1st and number of prenatal visits, marital status and history of preterm birth or SGA as confounders? Why did the authors choose epilepsy and folic acid as a potential confounding variables?
Response: All information on possible confounders was requested from each database, but not all studies had information on the possible confounders mentioned by the reviewer. Epilepsy and folic acid were included as confounders resulting from previous studies and the literature.

PRISMA guidelines provided.

Results:
300-302, 314-326, 319-320, 327-328 aORs include 1.0 and should not be interpreted as significant. Recommend authors discuss role of heterogeneity in the cautious interpretation of their results.
Response: We agree with the reviewer that the results should be interpreted with caution and we tried to do so throughout the manuscript. As we present effect estimates (odds ratios) with 95% CIs in the text, we only point readers to the potentially interesting results, but never say that any result is statistically significant (as we did not test and use p values). Where 1.0 is included in the CI, we usually point that out, e.g. by mentioning wide confidence intervals (lines 321, 335, 357-358, and 375) or confidence intervals including unity (line 356). We also removed the word 'only' from the phrase 'only slightly lower' (lines 329-330, 356, and 375) and changed the wording in lines 339-340 from 'were associated' to 'seemed to be associated' and in line 358 from 'increased risks' to 'possibly increased risks', to account for relatively low effect estimates and imprecision in the results. Heterogeneity among studies was taken into account by using one-stage random-effects models in the analyses and is now discussed in lines 416-422 in the discussion section.

Discussion:
390-420 Appreciate the authors thorough discussion of limitations.
Response: Thank you

446-449 Associations between SSRI use and preterm birth and low 5 minute APGAR in restricted group is no longer significant as CI includes 1.0.
Response: Please see our response above. In this particular instance, we use the phrase 'albeit with wider confidence intervals'.

Conclusion:
455-460 Given the heterogeneity of studies in this meta-analysis and wide CIs found in some of their results, suggest that the authors recommend further comparative research for this controversial topic; would suggest deleting "carefully selecting the type of antidepressant prescribed", especially as evaluation of SSRIs was done as a secondary outcome.
Response: Per suggestion of the reviewer we deleted the last part of this sentence and replaced it by: In addition, further research with detailed information on timing and severity of depressive symptoms and use of antidepressants during pregnancy is recommended (lines 496 – 498).

Figures and Tables: Figure 1. Sp "Asses" to "Assess"
Response: We corrected this typo in Figure 1.

References: Appropriate for study.

Response: Thank you

STATISTICS EDITOR COMMENTS:

General and Table 1: This is a large cohort of IPD level data and all subsets have large sample sizes.

Table 2: However, the risks and associations are either NS or the strength of association is quite modest. The statistical associations are largely due to the large sample sizes and there is no adjustment for multiple hypothesis testing, which would make some of the associations NS. The differences between cohorts with depression but with vs without antidepressant use are in some cases statistically significant, albeit again modest in degree. Since the samples are mostly quite large, the Authors should corroborate their analyses with a matching algorithm, in addition to the multivariable logistic method.
Table 3: Same issues as in Table 2 regarding mostly modest associations, no adjustment for multiple hypothesis testing and need to corroborate with matching approach.
Response: As you can see from several of our responses to the reviewers and in the revised version of the manuscript, we did our utmost to not overstate our – indeed mostly modest – results. As we presented our results as effect estimates with 95% confidence intervals instead of testing the differences and generating p-values (per the guidelines of the journal), we could not adjust for multiple testing. The latter is not common practise in epidemiologic studies (except for genetic and -omics epidemiology) anyway. If need be, we could use 98% or 99% confidence intervals, but that would decrease the comparability with other meta-analyses.
Given your suggestion of using a matching algorithm, we revisited our earlier idea of using propensity scores and dived into the literature. Reassuringly, previous studies comparing multivariable analyses and propensity score based methods in IPD meta-analyses showed consistent results (see e.g. Fox et al, PLoS ONE 2016). Although a methodological comparison of the two types of confounder adjustment methods is interesting, it is beyond the scope of this manuscript. If deemed necessary, however, we are certainly willing to conduct propensity score matching in sensitivity analyses, but that will make the paper more complex.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase 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:
A. OPT-IN: Yes, please publish our point-by-point response letter.

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. Each of your coauthors received an email from the system, titled "Please verify your authorship for a submission to Obstetrics & Gynecology." Each author should complete the eCTA if they have no yet done so.
Response: all authors were contacted and full disclosure is provided on the title page.

3. 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.
Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.
Response: We included race/ethnicity as a confounder only, using the classifications as originally used in the studies included in this IPD meta-analyses. Therefore, we are unable to provide a concise description of the data collection and classification of race/ethnicity in our methods, covering the 27 different studies. If you feel that we should nonetheless, we will try to obtain this information from the co-authors, but this may take some time. Alternatively, we could run our analyses again without including race/ethnicity as a confounder, but this may seem strange as the most original studies did.

4. 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://eur02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-obstetrics-data-definitions&data=04%7C01%7Cmarleen.vangelder%40radboudumc.nl%7C7bcb9235c0e7486ba38a08d8f5ee7f5c%7Cb208fe69471e48c48d87025e9b9a157f%7C1%7C0%7C637529752702794725%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=B1YI909%2BnrPhQMfAF6PqD%2F81lWf%2BLkikbdesEQgHRf8%3D&reserved=0 and the gynecology data definitions at https://eur02.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2Fpractice-management%2Fhealth-it-and-clinical-informatics%2Frevitalize-gynecology-data-definitions&data=04%7C01%7Cmarleen.vangelder%40radboudumc.nl%7C7bcb9235c0e7486ba38a08d8f5ee7f5c%7Cb208fe69471e48c48d87025e9b9a157f%7C1%7C0%7C637529752702804720%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=k4Edw4FF%2BOM3lPpD04BExgv1yLf81%2FhLzZRmarmShv8%3D&reserved=0. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.
Response: All definitions used comply with the standard definitions

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.
Response: The manuscript now counts 35 pages including 9 pages with references and 3 almost empty pages (pages 4, 34, and 35).

6. 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]."

7. 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 Reviews is 300 words. Please provide a word count.
Response: Abstract was checked and a word count was added at the end.

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://eur02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=04%7C01%7Cmarleen.vangelder%40radboudumc.nl%7C7bcb9235c0e7486ba38a08d8f5ee7f5c%7Cb208fe69471e48c48d87025e9b9a157f%7C1%7C0%7C637529752702804720%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=YmTvFEjwOA8NT1hTcGId8%2BNC8iTqHZXfCqHzdiS8r14%3D&reserved=0. 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.
Response: We comply with the rules for abbreviations.

9. 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.
Response: The words ‘and/or’ were replaced by ‘or’ throughout the manuscript.

10. ACOG is moving toward discontinuing the use of "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.
Response: Health care provider was changed to health care professional throughout the text.

11. 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%").
Response: We comply with the above, using only effect estimates with 95% confidence intervals.

12. Please review examples of our current reference style at https://eur02.safelinks.protection.outlook.com/?url=http%3A%2F%2Fong.editorialmanager.com%2F&data=04%7C01%7Cmarleen.vangelder%40radboudumc.nl%7C7bcb9235c0e7486ba38a08d8f5ee7f5c%7Cb208fe69471e48c48d87025e9b9a157f%7C1%7C0%7C637529752702804720%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=zbotOikl2d1KIzpDvjOgZBfKuiWJ8XqSVQJNx3Fqua8%3D&reserved=0 (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.

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Response: We updated the references to the current reference style of the journal.

13. Figure 1: Please check the n values in the second exclusion box to make sure they total to 202.
Response: Thank you for pointing out this mistake, which we corrected in the revised Figure 1.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

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Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.
Response: The figures were created in Microsoft Powerpoint.

14. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.
Response: We comply with the rules for supplemental files. As all studies mentioned in the appendices are included in the reference list of the manuscript, we did not supply a separate reference list for the Appendixes. Please let us know if we need to create an extra reference list.

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