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: Aug 23, 2019
To: "Yael Bar-Zeev" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1404

RE: Manuscript Number ONG-19-1404

Association between Prenatal Smoking and Gestational Diabetes Mellitus: PRAMS Secondary Data Analysis

Dear Dr. Bar-Zeev:

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 Sep 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for your work. Specific comments:

Abstract: the last line does not read well, we know of many risks of smoking, this is not the one reason we should counsel against it. Rather it could read that this is ANOTHER reason to promote cessation.

Introduction: line 96-7 this idea needs to be fully elaborated, does this mean cessation could impact GDM? What is the concern here?

Methods: line 104-5 surveillance projects are not interventional by definition and can not impact directly on outcomes.

Lines 109-11 it is unclear how this relates to this study? You aren't ooking at infant outcomes, correct? So I would just mention that twin and triplet pregnancies are included.

In describing this study here some basic data on response rates and completeness of data is appropriate either here or in results section.

Results: line 173: by starting with stating the GDM rate it implies the rest of the paragraph applies to the GDM subset, but I think it is actually referring to the whole data set. Can you make this clearer?

Lines 200-9 This paragraph is confusing, you stratified and found that all strata had increased risk? How was the stratification informative then?

Discussion: lines 215-6 I do not know that you truly showed a dose response effect. All levels of smoking increased risk. I don't think you truly did a statistical analysis sufficient to prove a true dose response.

Line 264-5: I would argue that women would be more likely to deny smoking in pregnancy than misclassify themselves as smokers, so this would be differential.
As you describe in the methods that twin and triplet pregnancies are included in this dataset, how might this have impacted GDM rates and is there a high enough proportion of these pregnancies to impact results?

Lines 273-5 again, this phrasing indicates that thi is now proof to encourage cessation, where as it is ANOTHER reason and should be stated as such.

Reviewer #2: This manuscript addresses interesting data about the details of smoking during pregnancy and gestational diabetes.

It will be easier for readership if the information data of controls were described in some details, how were they matched with patients who developed gestational diabetes.

Was this information about smoking in different trimesters of pregnancy available?

It is possible that some of the patients quit smoking or reduced when they were diagnosed to have gestational diabetes. This may be helpful in streamlining possible mechanism of the conclusion of the study.

Although the purpose of this study was to identify outcome variable pertaining to gestational diabetes alone, but were there any stillbirths and/or IUGR and then correlating this information with smoking, weight gain, etc.?

Possible mechanism of increased likelihood of gestational diabetes with smoking needs to be discussed in detail.
Are there any data in the controls about Never smokers or no smokers for years and those who just stopped in very early pregnancy?

Any difference in patients controlled on diet vs those controlled on Insulin or oral anti diabetic agent?

Reviewer #3: This is a study using information from retrospectively collected self-reported data, using the PRAMS data from 2009 - 2015. The purpose of the study is to document the association between smoking and GDM.
The strength of this study is that the numbers are high and that they supposedly are representative of the 'general population'. The weakness of course, that the questionnaires are filled out several months after the fact and that self-reporting increases the risk of recall bias; especially since smoking in pregnancy is a loaded subject.

1. 149-153. The authors explain in detail the IOM guidelines for weight gain in pregnancy for the different weight groups. Most obstetricians are familiar with these guidelines although not with the PRAMS data-set; a short explanation would be useful.

2. 174.... 11.8% of the participants.... There are 232,000 participants (173), 11.8% of these quit smoking? "11.8% of smokers" would be more precise.

3. 245-247 . ...suggest that the association between smoking and GDM, is independent of these two factors [GWG and pre-pregnancy weight]. Yet in 207-209 you say that [smoking] "was associated with higher odds of GDM only among women who were obese during pre-pregnancy or had excessive GWG". Now, which is it? Further you write (209) "data not shown". Why not?

4. 274-275 ." ....prenatal smoking should be strongly discouraged to reduce maternal risk of GDM". You have shown an association, not causation. While smoking cessation is to be discouraged for many reasons, this study does support that smoking cessation will reduce the risk of GDM.

STATISTICAL EDITOR'S COMMENTS:

1. lines 122-129: Need to include a flow diagram and enumerate how many women were excluded due to missing data. Were those exclusions for missing all covariates or only ≥ 1? If so, need to specify which covariates and the frequency of missing data. Could be supplemental material.

2. Table 1: Several of the (%)s cited in the Table are incorrect, most obviously "No HTN/Yes GDM" 12140(91.8%) should be 5.7%. The other 3 categories in that section are also incorrectly calculated. Please check all entries in this Table for accuracy and if there were missing data, then need to enumerate all. Need units for age, BMI and should specify categories of BMI. Need to clarify "weighted percent". It appears to be % based using overall row total in 2nd column as denominator.

3. Table 2: Need units for age, BMI and should specify categories of BMI. Need to include in footnote a list of covariates included in the final model for aORs.

4. Tables 3, 4: Need to include Crude ORs for contrast with aORs and need to include (could be a separate Table), the counts for the various subsets described. Need to include in footnote a list of covariates included in the final model for aORs and justify the number of variables included in the aOR models vs the counts of GDM (the outcome) among the 12 and (16) subsets cited in the Table.

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.
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2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the 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.

3. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. 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), 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, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

5. 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 and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. 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 22 typed, double-spaced pages (5,500 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.

7. 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).

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

9. 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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

10. 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.

11. 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.

12. 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%").

13. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

14. 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.

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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.

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 Sep 13, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

[redacted]

16/09/2019

Manuscript Number ONG-19-1404
Association between Prenatal Smoking and Gestational Diabetes Mellitus: PRAMS Secondary Data Analysis

Dear Editorial Team,
Obstetrics and Gynecology

We thank 'Obstetrics and Gynecology' for giving us the opportunity to resubmit this manuscript, and we thank the reviewers for their constructive comments.

We confirm that we have read the instructions for authors and respond below to the comments on a point-by-point basis. Changes are shown in track changes in the text. We hope you will find our responses satisfactory, and hope that you will find this manuscript acceptable for publication in your journal.

This study uses a secondary data analysis from the Pregnancy Risk Assessment Monitoring System (PRAMS) database – for this database, data collection and entry is performed by states health department staff or by professional survey research organizations contracted by the health department. A number of quality control measures are employed to ensure data validity. Data entry verification is required for a minimum of 10% of mail surveys (100% verification of mail surveys is performed in many states). To ensure telephone surveys are properly administered and recorded, a minimum of 10% of all calls are monitored by supervisors.

On behalf of all the authors,

Dr Yael Bar Zeev
Braun School of Public Health and Community Medicine
The Hebrew University of Jerusalem -Hadassah Medical Centre
yael.bar-zeev@mail.huji.ac.il

[redacted]

Reviewer 1

1. Abstract: the last line does not read well, we know of many risks of smoking, this is not the one reason we should counsel against it. Rather it could read that this is ANOTHER reason to promote cessation.

Response:

This has been amended as requested: *"Reducing smoking during pregnancy may reduce the risk of GDM and could serve as an additional approach towards promoting smoking cessation among pregnant women."*

2. Introduction: line 96-7 this idea needs to be fully elaborated, does this mean cessation could impact GDM? What is the concern here?

Response:

Yes, the concern is that both continuing to smoke during pregnancy, and possibly also smoking cessation, might each increase the risk of GDM.

This has been clarified in lines 20-26: *"Prenatal smoking has not been conclusively identified as a factor associated with GDM, with studies showing mixed results. In addition, smoking cessation may increase appetite, and weight gain, which are associated with GDM. In the general non-pregnant population, smoking cessation has also been shown to increase the risk of type 2 diabetes in the first few years following cessation, independent of post-cessation weight gain. Therefore, both smoking, and smoking cessation in the short term, might increase the risk of developing GDM."*

3. Methods: line 104-5 surveillance projects are not interventional by definition and can not impact directly on outcomes.

Response:

This has been amended – lines 33-34: *"PRAMS is a surveillance project designed to monitor maternal attitudes and experiences before, during, and shortly after pregnancy."*

4. Lines 109-11 it is unclear how this relates to this study? You aren't looking at infant outcomes, correct? So I would just mention that twin and triplet pregnancies are included.

[redacted]

Response:

We have now changed the analysis to include only singleton pregnancies (see also comment 10). Therefore, this has been amended, lines 44: *"Only singleton pregnancies were included."*

5. In describing this study here some basic data on response rates and completeness of data is appropriate either here or in results section.

Response:

Unfortunately, we do not have these specific data for the PRAMS dataset. The PRAMS sample of women who have had a recent live birth is drawn from each participating state's birth certificate files. Each participating state draws a stratified systematic sample of 100 to 250 new mothers every month from a frame of eligible birth certificates. Most states oversample low weight births. Many states stratify by mother's race or ethnicity as well. Annual sample sizes range from 1000 to 3400, divided among three to six strata, for each participating state. Nonresponse adjustment factors attempt to compensate for the tendency of women having certain characteristics (such as being unmarried or of lower education) to respond at lower rates than women without those characteristics. A full description of the methodology for the PRAMS can be found here:

https://www.cdc.gov/prams/methodology.htm

This information has been added in lines 37-44.

6. Results: line 173: by starting with stating the GDM rate it implies the rest of the paragraph applies to the GDM subset, but I think it is actually referring to the whole data set. Can you make this clearer?

Response:

This has been clarified that it is actually referring to the whole data set, lines 115-116: *"Among all of the participants, the vast majority were non-smokers for more than two years prior to their pregnancy (75.0%)"*

7. Lines 200-9 This paragraph is confusing, you stratified and found that all strata had increased risk? How was the stratification informative then?

Response:

The stratification shows that there is no effect modification, since the association between prenatal smoking and GDM is consistent among all of the strata. This

[redacted]

provides further evidence that the association between prenatal smoking and GDM is independent of prepregnancy BMI and GWG (in addition to controlling for these covariates in the multivariate model).

8. Discussion: lines 215-6 I do not know that you truly showed a dose response effect. All levels of smoking increased risk. I don't think you truly did a statistical analysis sufficient to prove a true dose response.

Response:

Thank you for this comment and we agree with it. We have changed this now to be more suggestive, lines 158-159: *"The results are suggestive that the positive association between smoking and GDM might be linked in a dose response relationship."*

9. Line 264-5: I would argue that women would be more likely to deny smoking in pregnancy than misclassify themselves as smokers, so this would be differential.

Response:

We agree that women would be more likely to deny smoking. The concern was that there would be a difference in the proportion of women denying smoking in the two sub-populations – those with GDM and those without. If this misclassification as non-smokers (due to women denial) is different between these two sub-populations, it can impact the OR of the association. However, we do not feel there is a reason to believe that the proportion of women denying their smoking status to be different between women with or without GDM.

This has been clarified in lines 222-224: *"Similarly, smoking status was defined based on self-report and was not biochemically validated. However, it is unlikely that misclassification was differential among women with or without GDM."*

10. As you describe in the methods that twin and triplet pregnancies are included in this dataset, how might this have impacted GDM rates and is there a high enough proportion of these pregnancies to impact results?

Response:

Almost all of the sample is singleton pregnancies (98.2%), with only 1.7% twins and 0.04% triplets. However, we agree that twin and triplet pregnancies may impact GDM rates, and since we do not have a big enough sample to add this as a separate variable, we have decided to exclude pregnancies that are not singleton. We have re-

[redacted]

run the analysis using only singleton pregnancies and have corrected the manuscript and tables accordingly.

11. Lines 273-5 again, this phrasing indicates that this is now proof to encourage cessation, where as it is ANOTHER reason and should be stated as such.

Response:

This has been amended as requested, lines 232-234: *"Considering that irrespective of GWG or pre-pregnancy BMI, smoking was independently associated with GDM, reducing the risk of GDM can be considered as an additional reason for strongly discouraging prenatal smoking"*

Reviewer 2

12. It will be easier for readership if the information data of controls were described in some details, how were they matched with patients who developed gestational diabetes.

Response:

The PRAMS has a cross-sectional design (and not a case-control study design) – women are requested to answer the PRAMS survey 2-4 months after delivery. Therefore, there is no matching between women who develop gestational diabetes and those who did not.

13. Was this information about smoking in different trimesters of pregnancy available?

Response:

Unfortunately, no. The PRAMS survey only included questions regarding the amount smoked in the three months prior to becoming pregnant, and the last three months of the pregnancy.

We have added this as a limitation in lines 213-215: *"Additionally, we did not have data on women's smoking status throughout the different pregnancy trimesters, which would have abled us to differentiate between early and late smoking cessation, and whether this impacted the risk for GDM."*

14. It is possible that some of the patients quit smoking or reduced when they were diagnosed to have gestational diabetes. This may be helpful in streamlining possible mechanism of the conclusion of the study.

Response:

[redacted]

That is a possibility. However, since this is a cross-sectional data, temporal sequence cannot be established. This is one of the limitations of this study.

15. Although the purpose of this study was to identify outcome variable pertaining to gestational diabetes alone, but were there any stillbirths and/or IUGR and then correlating this information with smoking, weight gain, etc.?

Response:

Thank you for this comment. PRAMS collects data from women who have had a live birth, therefore women who experienced stillbirth are not included. Data on IUGR are not captured.

16. Possible mechanism of increased likelihood of gestational diabetes with smoking needs to be discussed in detail.

Response:

We have added more detail in this regard to the discussion, line 164-171: *"The higher risk of GDM among pregnant women who smoke is probably mediated through the same physiological mechanisms that underlie the higher risk of diabetes in people who smoke, which includes insulin resistance and impaired glucose hemostasis. The exact biologic mechanism for this is not completely understood but it is suggested that this is partially caused by an increased risk of central obesity, and increases in oxidative stress and endothelial disfunction. In addition, animal and human studies have found that nicotine can reduce the release of insulin through direct activation of nicotinic receptors on pancreatic islet cells."*

17. Are there any data in the controls about Never smokers or no smokers for years and those who just stopped in very early pregnancy?

Response:

Thank you for this comment. Indeed, there is data differentiating between those who have not smoked for more than two years before their birth, and those who quit before pregnancy (did not smoke during the 3 months prior to pregnancy). We have now updated the analysis and differentiated between these two groups (lines 76-84).

[redacted]

18. Any difference in patients controlled on diet vs those controlled on Insulin or oral anti diabetic agent?

Response:

Unfortunately, this information was not collected as part of the PRAMS survey.

Reviewer 3

19. 149-153. The authors explain in detail the IOM guidelines for weight gain in pregnancy for the different weight groups. Most obstetricians are familiar with these guidelines although not with the PRAMS data-set; a short explanation would be useful.

Response:

Thank you for this comment. We prefer to leave the detailed IOM guidelines as we think this is necessary for the readers understanding, and not all readers would be obstetricians.

We have added more information regarding the PRAMS dataset (lines 35-57), as also requested by reviewer 1 in comment number 5 (see above).

20. 174.... 11.8% of the participants.... There are 232,000 participants (173), 11.8% of these quit smoking? "11.8% of smokers" would be more precise.

Response:

We have amended this as requested, line 116-117: *"Among the participants who smoked, 11.8% of the participants quit smoking during pregnancy…"*

21. 245-247 . ...suggest that the association between smoking and GDM, is independent of these two factors [GWG and pre-pregnancy weight]. Yet in 207-209 you say that [smoking] "was associated with higher odds of GDM only among women who were obese during pre-pregnancy or had excessive GWG". Now, which is it? Further you write (209) "data not shown". Why not?

Response:

We have clarified that this independent association was only among women who smoke the same or more cigarettes per day, line 196-198: *"Furthermore, our stratified analysis according to GWG and pre-pregnancy BMI, further suggest that*

[redacted]

the association between smoking and GDM, is independent of these two factors for those who continue to smoke the same or more cigarettes a day."

We have now included the additional sub-analysis grouping the smoking status by number of cigarettes smoked per day during pregnancy in supplemental file 2.

22. 274-275 ." ....prenatal smoking should be strongly discouraged to reduce maternal risk of GDM". You have shown an association, not causation. While smoking cessation is to be discouraged for many reasons, this study does support that smoking cessation will reduce the risk of GDM.

Response:

Thank you for this comment and we agree. Therefore, we have amended the sentence, line 232-234: *"Considering that irrespective of GWG or pre-pregnancy BMI, smoking was independently associated with GDM, this can be considered as an additional reason for discouraging prenatal smoking."* We also acknowledge the fact that we have not proven causation in the next paragraph (lines 238-241) calling for more definitive research – "*A large prospective cohort study, collecting data on all known risk factors and possible confounders of GDM, with biochemical validation of GDM and smoking status, is needed to provide a more definitive answer on the direct casual association between prenatal smoking and GDM, and the interplay with GWG."*

Statistical Editor

23. lines 122-129: Need to include a flow diagram and enumerate how many women were excluded due to missing data. Were those exclusions for missing all covariates or only ≥ 1? If so, need to specify which covariates and the frequency of missing data. Could be supplemental material.

Response: We have added figure one which includes a flow diagram as recommended. We excluded those with missing data on any covariates adjusted in the multivariable models. We have also included a new supplementary table S6 showing distribution of missing data and comparison of those who were included the final analytic sample to those who were excluded due to missing data on covariates adjusted in the multivariable models. We have added this to the discussion, line 216-220:

"We excluded participants with missing data on covariates (n= 5375), which could have impacted the final results. Our final sample included a higher proportion of participants with normal or excessive GWG, were non smokers for over 2 years

[redacted]

prior to their pregnancy, or were "non-Hispanic white" ethnicity (supplemental file 3). Therefore, this might have amplified the actual ORs between prenatal smoking and GDM."

24. Table 1: Several of the (%)s cited in the Table are incorrect, most obviously "No HTN/Yes GDM" 12140(91.8%) should be 5.7%. The other 3 categories in that section are also incorrectly calculated. Please check all entries in this Table for accuracy and if there were missing data, then need to enumerate all. Need units for age, BMI and should specify categories of BMI. Need to clarify "weighted percent". It appears to be % based using overall row total in 2nd column as denominator.

Response:

We have checked the data and corrected where needed. We have also added the units for age and BMI, and specified the BMI categories. We used weighted percent to adjust for complex sample design. We have now included this as a footnote on table 1. As we excluded participants with missing data on covariates (figure 1), there is no missing data in the table.

25. Table 2: Need units for age, BMI and should specify categories of BMI. Need to include in footnote a list of covariates included in the final model for aORs

Response:

This information has been added to the table.

26. Tables 3, 4: Need to include Crude ORs for contrast with aORs and need to include (could be a separate Table), the counts for the various subsets described. Need to include in footnote a list of covariates included in the final model for aORs and justify the number of variables included in the aOR models vs the counts of GDM (the outcome) among the 12 and (16) subsets cited in the Table.

Response:

We have included in supplemental file 1 the Crude ORs for tables 3 and 4, and have clarified this in the manuscript text. The sample sizes for each sub-group are provided. We have also added in a footnote a list of the covariates included in the final model. We used the purposeful selection process to retain only variables with a significant bivariate test at a $p<0.05$ in the multivariable analyses.