

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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obgyn@greenjournal.org.

Date: Aug 14, 2019
To: "Ya-Hui Yu" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1378

RE: Manuscript Number ONG-19-1378

The effect of developing obesity between pregnancies on stillbirth and infant mortality in a cohort of multiparous women

Dear Dr. Yu:

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 03, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective cohort review whose main objective is to evaluate the effect of new onset pre-pregnancy obesity on stillbirth and infant mortality. The authors abstracted data from a statewide database that identified women who had at least 2 pregnancies and who were of normal weight at the start.

Disclosures: NIH supported study.

Human subjects: IRB approval was obtained from the University of Pittsburgh.

Abstract:

1. The abstract is specific and representative of the article, well written.

Introduction:

2. The problem is stated and a brief background review provided. The authors note that while obesity is common, it is a complex disorder with multiple sub-phenotypes. There is limited data on timing of obesity relative to pregnancy outcomes.

Methods:

3. Lines 121-124: Were deaths due to anomalies included in the sample?
4. Line 126: Were both weight and height self-reported? Also it may be useful to describe when in the gestational period the pregnancy BMI was ascertained.

Results:

5. Lines 191-195: Women who became underweight in their second pregnancy had excess stillbirths (2.9, 95% CI: 0.5, 5.3, although CI includes 0). Has this been noted elsewhere in the literature, is there a potential mechanism for this?
6. Lines 200-201: This may seem like a simple question but please help the readers understand what the U-shaped relationship means. Do we interpret negative BMI changes to also increase risk of stillbirth and infant death?

Discussion:

7. Very well written discussion section with helpful review of existing literature. Interesting speculation that BMI

increase in women with shorter inter-pregnancy intervals may indicate postpartum weight retention

8. Perhaps the authors can add to the discussion section their thoughts on the findings related to becoming underweight and risk of death.

References:

9. The reference list is very extensive and appears complete.

TABLES and FIGURES:

10. It might be useful to include eFigure 3s in the main paper as postneonatal mortality is a primary outcome of interest.

Reviewer #2: The authors conducted a large cohort study assessing the associations between newly developed underweight, overweight, or obesity and stillbirth and mortality in offspring. They used a population-based cohort that linked birth registry and death records in Pennsylvania. After adjustment for relevant covariates, the authors found significant associations of women who had newly developed underweight and newly developed obesity with risk of stillbirth and/or infant and neonatal mortality. No significant associations were observed with BMI transitions between pregnancies and postneonatal mortality. The authors did a nice job of explaining and interpreting complex associations in a clear and succinct manner. Overall, the study was well executed and written up. I have made comments below that I hope the authors find useful to improve their well-developed manuscript.

1. Title: I would encourage the authors to not use the word 'effect' in the title given this is not an experimental study.
2. Line 93 (and elsewhere): There are a few typos (e.g., 2106) and errors throughout the manuscript.
3. Line 116: The authors should clarify what they mean by 'questionable data.'
4. Line 125: What type of bias, as a result of misclassification, does including self-reported data have on the outcomes of the study?
5. Lines 150-2: The authors should comment on how data imputation potentially impacts their results. What type of missing data patterns did the authors observe (e.g., missing at random)?
6. Lines 175-6: Did the authors explore other IPIs besides less than 18 months and greater than or equal to 18 months? If so, did that modify their findings?
7. Methods: Did the authors adjust for GWG in the first pregnancy? Note: I appreciate the authors using appropriate measures of association (risk ratios) for their study (not logistic regression and odds ratios).
8. Table 2: I encourage the authors to utilize a table footer to describe what covariates were adjusted for in their analyses.
9. Figure 1: The flow diagram is not very clear. For instance, why does the middle box of women with normal weight in 1st pregnancy have two samples? Is one for the stillbirth analytic cohort and the other for the infant mortality cohort? What does the asterisk mean? These factors should be clarified.
10. General Comment 1: If the intent of the manuscript is to study developing obesity, why did the authors choose to retain and analyze women who transitioned from normal weight to underweight between pregnancies?
11. General Comment 2: Did the authors analyze nulliparous normal weight women or just the first pregnancy that was recorded in the dataset? If the latter, would it not be a 'cleaner' analysis to focus on nulliparous women and avoid previous pregnancies, pregnancy complications, experiencing GWG and postpartum weight loss, retention, or gain, and other factors?
12. Major Comment 1: In order to reduce adverse outcomes in offspring, the authors advocate for mothers to have proper GWG and postpartum weight loss. This is of course easier said than done. Interventional studies have rendered less than desirable results for reducing GWG and PPWR. I would encourage the authors to provide context of these challenges, and potentially, how individuals can overcome this.
13. Major Comment 2: The authors correctly note that duration of obesity has an influence on adverse outcomes. To further test this, in the context of the outcomes in this study, why did the authors not explore women who transitioned from normal weight to obese vs. women who entered pregnancy obese and retained that BMI status?

Reviewer #3: Most studies use BMI before pregnancy without reference to the duration of exposure to obesity. The reason and the time when the woman became obese are very variable elements and if we want to reduce the risks related to

maternal obesity it is necessary to better understand these different situations. It is a clear, interesting and well-written paper even if the statistical tools are difficult to follow in the methods even for a reader accustomed to methods a little advanced.

I have some remarks

1 It is important not to include intermediate factors and associated pathology in multivariate analyzes. However, to explain the association found, it would have been interesting to study the responsibility of certain factors and pathologies in the occurrence of a stillbirth. I understand that it is not the purpose of this paper that is already dense but a point of discussion on this issue would be interesting.

2 In the same way, if these weight gain changes are not directly involved in perinatal accidents, doing a program to avoid weight gain between two pregnancies may not have an impact. Thus, these modifications of the BMI could be simply an intermediate factor. This question about the potential benefits of this study deserves to be discussed.

3 Please, Give the meaning of the abbreviations in Table 1 in footnotes (DM and HTN).

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: In this Table, need to test for statistical differences by row characteristic between normal wgt vs the other three categories.

2. Table 2, lines 132-140: It appears that > 20 variables were included in the adjustment model. Contrast this with the counts for stillbirth, infant, neonatal or post natal mortality among the underwgt, and obese cohorts and the likelihood of over fitting the model is high. Given the size of the control group, a matching algorithm should be done to corroborate the associations found.

Associate Editor's Comments:

In your revision please

- 1) Remove causal language
- 2) As suggested by reviewer, please corroborate your findings with a matching algorithm.

EDITOR COMMENTS:

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

*The manuscript's guarantor.

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

4. 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.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 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.

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

9. 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).

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

11. 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."

12. 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.

13. 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.

14. 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.

15. 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%).

16. 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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18. The Production Editor had the following to say about these figures:

"Figure 1: Please upload the figure as a separate figure file on Editorial Manager. Additionally, please consider reworking the bottom of the flowchart (below women with normal weight in first pregnancy) to be more clear. It is difficult to follow the n values between the single exclusion box and the analyses.

Figure 2: Please upload the figure as a separate figure file on Editorial Manager. "

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.

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Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

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 03, 2019, we will assume you wish to withdraw the manuscript from further consideration.

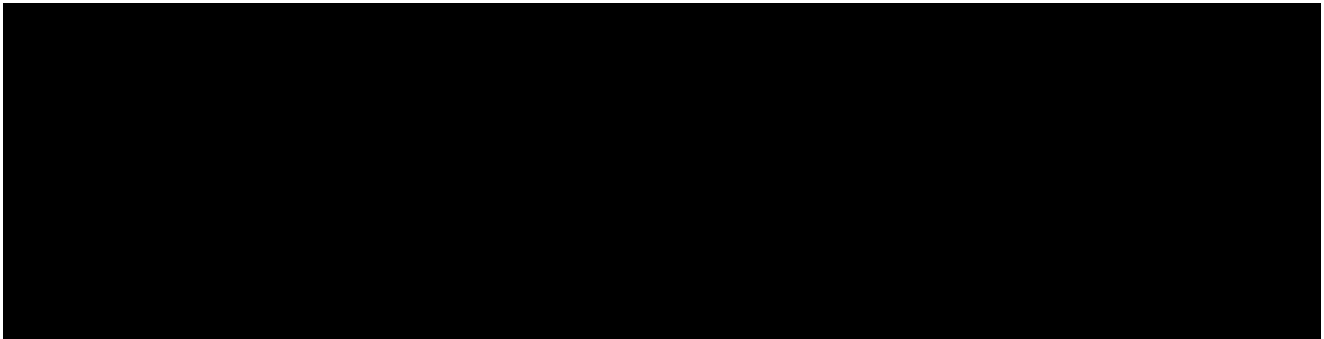
Sincerely,

The Editors of Obstetrics & Gynecology

2018 IMPACT FACTOR: 4.965

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

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Nancy C. Chescheir, MD
Editor-in-Chief
Obstetrics & Gynecology

Re: “The effect of developing obesity between pregnancies on stillbirth and infant mortality in a cohort of multiparous women”

Dear Dr. Chescheir,

We are re-submitting the above manuscript for consideration for publication as an Original Article. We are grateful for the feedback and comments from the editor and reviewer. We have improved our manuscript and provided point-by-point responses attached in the end of this cover letter.

As the lead author of this manuscript, I affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. All authors have approved the manuscript, contributed significantly to the work, and there are no conflicts of interest from any of the co-authors.

On behalf of the co-authors, we thank the editors for considering this paper.
Please address questions and correspondence to me.

Sincerely,
Ya-Hui Yu



Response to the comments from the reviewers and editor

Obstetrics & Gynecology (ONG-19-1378): The effect of developing obesity between pregnancies on stillbirth and infant mortality in a cohort of multiparous women

REVIEWER COMMENTS:

REVIEWER #1

This is a retrospective cohort review whose main objective is to evaluate the effect of new onset pre-pregnancy obesity on stillbirth and infant mortality. The authors abstracted data from a statewide database that identified women who had at least 2 pregnancies and who were of normal weight at the start.

Disclosures: NIH supported study.

Human subjects: IRB approval was obtained from the University of Pittsburgh.

Abstract:

1. The abstract is specific and representative of the article, well written.

Introduction:

2. The problem is stated and a brief background review provided. The authors note that while obesity is common, it is a complex disorder with multiple sub-phenotypes. There is limited data on timing of obesity relative to pregnancy outcomes.

Methods:

R1.1: Lines 121-124: Were deaths due to anomalies included in the sample?

Response to R1.1: No. Infant mortality was defined as the death of non-anomalous live-born infants before the age of 1 year. We further clarify this in the method section of the revision (p.4) as the following:

“infant mortality, defined as the death of non-anomalous live-born infants at <365 days.”

R1.2: Line 126: Were both weight and height self-reported? Also it may be useful to describe when in the gestational period the pregnancy BMI was ascertained.

Response to R1.2: Yes, both weight and height are self-reported and data were obtained via interviewing the mother before discharge from the hospital. We have added the following sentence in the method section of the revision (p.4):

“Both weight and height were obtained from interviewing mothers before discharge from hospitals.”

Results:

R1.3: Lines 191-195: Women who became underweight in their second pregnancy had excess stillbirths (2.9, 95% CI: 0.5, 5.3, although CI includes 0). Has this been noted elsewhere in the literature, is there a potential mechanism for this?

Response to R1.3: Becoming underweight among women who were normal weight at their first pregnancy has been linked to several adverse pregnancy outcomes (e.g. SGA or preterm birth) but not to stillbirth. We have added a paragraph in the discussion section of the current revision (p.10) for the potential explanation as follows:

“Contrary to previous literature^{26–28}, we found increased risk of stillbirth among women who became underweight after being normal weight in a previous pregnancy. The plausible mechanisms remain unclear. Interpregnancy weight loss may affect changes in placental function due to evidence suggesting a relation with lower placenta weight³². However, these findings may also be affecting by unmeasured risk factors like underlying illness or psychosocial factors.”

R1.4: *Lines 200-201: This may seem like a simple question but please help the readers understand what the U-shaped relationship means. Do we interpret negative BMI changes to also increase risk of stillbirth and infant death?*

Response to R1.4: Yes, a U-shaped relationship suggests that negative BMI changes increase the risk of stillbirth and infant mortality. To clarify, we have rephrased the sentence as follows (p.8):

“There was a U-shaped relation between interpregnancy BMI change for the risks of stillbirth and infant death, with the lowest risks at BMI change of 0 to 2 units (Figure 2, Panels A and B). Risks of both outcomes rose sharply as BMI increased beyond 2-kg/m² (equivalent to an average interpregnancy weight gain of 5 kg for women with 160 cm height). These risks also increased when BMI decreased between two pregnancies.”

Discussion:

7. Very well written discussion section with helpful review of existing literature. Interesting speculation that BMI increase in women with shorter inter-pregnancy intervals may indicates postpartum weight retention

R.1.5: *Perhaps the authors can add to the discussion section their thoughts on the findings related to becoming underweight and risk of death.*

Response to R1.5: Please refer to response to R1.3.

References:

9. The reference list is very extensive and appears complete.

Tables and figures:

R1.6: *It might be useful to include eFigure 3s in the main paper as postneonatal mortality is a primary outcome of interest.*

Response to R1.6: Thanks for the suggestion. We moved eFigure 2s (dose response curve of prepregnancy BMI and interpregnancy BMI change with risk of neonatal and post neonatal mortality) to the main paper as Figure 3 in this revision.

REVIEWER #2

The authors conducted a large cohort study assessing the associations between newly developed underweight, overweight, or obesity and stillbirth and mortality in offspring. They used a population-based cohort that linked birth registry and death records in Pennsylvania. After adjustment for relevant covariates, the authors found significant associations of women who had newly developed underweight and newly developed obesity with risk of stillbirth and/or infant and neonatal mortality. No significant associations were observed with BMI transitions between pregnancies and postneonatal mortality. The authors did a nice job of explaining and interpreting complex associations in a clear and succinct manner. Overall, the study was well executed and

written up. I have made comments below that I hope the authors find useful to improve their well-developed manuscript.

R2.1: Title: *I would encourage the authors to not use the word 'effect' in the title given this is not an experimental study.*

Response to R2.1: We changed the title as the following:

“The association of developing obesity between pregnancies with stillbirth and infant mortality in a cohort of multiparous women”

R2.2: Line 93 (and elsewhere): *There are a few typos (e.g., 2106) and errors throughout the manuscript.*

Response to R2.2: Thanks for bringing these to our attention. We corrected the typos in the revision.

R2.3: Line 116: *The authors should clarify what they mean by 'questionable data.'*

Response to R2.3: We were referring to ages that were not logical (e.g. younger age at second pregnancy) or negative interpregnancy intervals. We further explained it in the method section of the revision (p.4) as the following:

“Women with questionable data (illogical age or interpregnancy intervals) or prior twin gestations were excluded.”

R2.4: Line 125: *What type of bias, as a result of misclassification, does including self-reported data have on the outcomes of the study?*

Response to R2.4: Our results may be subject to bias from misclassification of BMI categories since prepregnancy weight and height were self-reported. However, when accounting for the misclassification of BMI in one of our previous studies examining the association of maternal obesity and infant mortality¹, there were no meaningful differences found in the study results. We had addressed this issue in the discussion section as one of our key limitations (p.10):

“BMI calculated from self-reported height and weight may result in misclassification³². However, previous studies analyzing this cohort showed that after accounting for misclassification, the relations between prepregnancy obesity and infant mortality were not meaningfully different¹².”

R2.5: Lines 150-2: *The authors should comment on how data imputation potentially impacts their results. What type of missing data patterns did the authors observe (e.g., missing at random)?*

Response to R2.5: We observed a non-monotone missing pattern in our data and we assumed our data was missing at random. In brief, we imputed these missing data 10 times using multiple imputation via chained equations. Our imputation models included variables of analytic interest without missing values (year of birth, infant death/stillbirths, breastfeeding intentions etc.) as well as several auxiliary variables (mother ID, county-level federal information processing standards codes, census tract, facility code etc.) to impute missing values on several variables (e.g. prepregnancy weight and height, weight at delivery, age, race/ethnicity, parity, smoking

status prior to pregnancy etc.). There was no meaningful difference shown in the previous study results when using the completed data versus multiple imputation analysis¹. Due to the limited space, the detailed information can be found in the previous literature and have been referred to in method section of the current manuscript.

R2.6: *Lines 175-6: Did the authors explore other IPIs besides less than 18 months and greater than or equal to 18 months? If so, did that modify their findings?*

Response to R2.6: Yes, we also explored the impact of short IPI defined as less than 6 months or less than 12 months. Both of these results showed similar patterns as those results of short IPI defined as less than 18 months but yielded very wide confidence intervals.

R2.7: *Methods: Did the authors adjust for GWG in the first pregnancy? Note: I appreciate the authors using appropriate measures of association (risk ratios) for their study (not logistic regression and odds ratios).*

Response to R2.7: No, we did not adjust for GWG in the first pregnancy since the prepregnancy BMI of second pregnancy is highly correlated with GWG in the first pregnancy. In fact, in our preliminary analyses that included GWG in the first pregnancy, we discovered several model convergence problems and non-overlapping propensity scores (suggesting positivity violations).

R2.8: *Table 2: I encourage the authors to utilize a table footer to describe what covariates were adjusted for in their analyses.*

Response to R2.8: Thanks for the suggestion. We added table footers in the current revision as the following:

“Covariates adjusted in the model: maternal race/ethnicity, height, parity, inter-pregnancy interval between current and last pregnancies; variables of prior and current pregnancies: maternal age, education, urban residence, percent Black residents, prepregnancy diabetes, prepregnancy hypertension, smoking status, marital status and insurance of current and prior pregnancy; variables of prior pregnancy: gestational diabetes, gestational hypertension, smoking status during pregnancy, gestational age, birth weight, birth facility level of neonatal care, neonatal intensive care unit admission, Women, Infants, and Children program usage, breast feeding, mode of delivery, apgar score, stillbirth, and infant death”

R2.9: *Figure 1: The flow diagram is not very clear. For instance, why does the middle box of women with normal weight in 1st pregnancy have two samples? Is one for the stillbirth analytic cohort and the other for the infant mortality cohort? What does the asterisk mean? These factors should be clarified.*

Response to R2.9: Thank you for raising these points. We improved the flow chart in the revision to better demonstrate that the analytic cohort for stillbirth analysis was from 2006 to 2013 while the infant mortality analysis was from 2003 to 2013 (details in the method section). Please let us know if there is anything need to be clarified.

R2.10: *General Comment 1: If the intent of the manuscript is to study developing obesity, why did the authors choose to retain and analyze women who transitioned from normal weight to underweight between pregnancies?*

Response to R2.10: Due to little evidence of the risk of stillbirth and infant mortality among this group in the literature, we decided not to exclude the results of this group in our manuscript.

R2.11: *General Comment 2: Did the authors analyze nulliparous normal weight women or just the first pregnancy that was recorded in the dataset? If the latter, would it not be a 'cleaner' analysis to focus on nulliparous women and avoid previous pregnancies, pregnancy complications, experiencing GWG and postpartum weight loss, retention, or gain, and other factors?*

Response to R2.11: Because we used administrative data, we cannot pinpoint the exact timing of obesity onset. However, we opted for the next best thing, which was to create a dataset in which the onset of obesity was known within bounds. This does allow us to rule out the potential impact that, for example, decades-long obesity may have on our outcomes of interest. However, we agree with the reviewer, were the data available, it would be highly interesting to evaluate the impact of newly-developed obesity on nulliparous women.

R2.12: *Major Comment 1: In order to reduce adverse outcomes in offspring, the authors advocate for mothers to have proper GWG and postpartum weight loss. This is of course easier said than done. Interventional studies have rendered less than desirable results for reducing GWG and PPWR. I would encourage the authors to provide context of these challenges, and potentially, how individuals can overcome this.*

Response to R2.12: Thanks for the suggestions. Indeed, we agree that suggesting intervening to change GWG is much easier than actually changing GWG. Unfortunately, this issue is quite complex, is not the focus of the current paper, and has been covered in some depth in prior research. Thus, we have added the following to the discussion section, in an attempt to address these concerns:

“Pregnancy presents a motivating opportunity for a healthy lifestyle; however, the major physical and social role changes complicate potential interventions. It is important to consider how to tailor interventions to meet personal needs and how to translate of results of trials into the formal clinical guidelines^{42,43}.”

R2.13: *Major Comment 2: The authors correctly note that duration of obesity has an influence on adverse outcomes. To further test this, in the context of the outcomes in this study, why did the authors not explore women who transitioned from normal weight to obese vs. women who entered pregnancy obese and retained that BMI status?*

Response to R2.13: Please refer to the response to R2.11.

REVIEWER #3

Most studies use BMI before pregnancy without reference to the duration of exposure to obesity. The reason and the time when the woman became obese are very variable elements and if we want to reduce the risks related to maternal obesity it is necessary to better understand these different situations. It is a clear, interesting and well-written paper even if the statistical tools are difficult to follow in the methods even for a reader accustomed to methods a little advanced.

I have some remarks

R3.1: *It is important not to include intermediate factors and associated pathology in multivariate analyzes. However, to explain the association found, it would have been interesting to study the responsibility of certain factors and pathologies in the occurrence of a stillbirth. I understand that it is not the purpose of this paper that is already dense but a point of discussion on this issue would be interesting.*

Response to R3.1: Thanks for the suggestion. We added the following sentence and two new references in the discussion section (p.9) of the current revision. We hope this edit addresses your concern:

“Although the literature does not examine underlying mechanisms of newly-developed obesity, cumulative evidence in prepregnancy obesity suggests several plausible explanations including placental dysfunction, inflammation and metabolic abnormalities^{30,31}.”

R3.2: *In the same way, if these weight gain changes are not directly involved in perinatal accidents, doing a program to avoid weight gain between two pregnancies may not have an impact. Thus, these modifications of the BMI could be simply an intermediate factor. This question about the potential benefits of this study deserves to be discussed.*

Response to R3.2: We agree that different approaches to modify BMI status may have different impact on the risk of stillbirth. We have further elaborated this issue in the discussion section (p.11) of the current revision as the following:

“Different approaches for weight maintenance likely have different impacts on reducing risk of adverse outcomes. To develop effective interventions for weight maintenance to prevent stillbirth and infant mortality, future studies focusing on understanding the reasons for becoming obese are warranted.”

R3.3: *Please, Give the meaning of the abbreviations in Table 1 in footnotes (DM and HTN).*

Response to R3.3: We spelled out these two terms in Table 1 of the revision.

STATISTICAL EDITOR'S COMMENTS

S1.1: *Table 1: In this Table, need to test for statistical differences by row characteristic between normal wgt vs the other three categories.*

Response to S1.1: Thanks for the suggestion. However, we decided not to test for statistical difference for Table 1 in the current revision for the following reasons:

- (1) Statistical significance represents impact from the combination of sample size and effect size. In large samples (like in our study), statistical significance may not reflect meaningful clinical differences^{4,5}.
- (2) The approach we used to choose confounders in our study was based on causal diagram gathering the prior knowledge and experts' opinion on the subject matters rather than based on selecting variables with statistical significance in Table 1.
- (3) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) is one of the guidelines referred in the author instructions of Obstetrics & Gynecology. It is

noted in the STROBE guideline-point 14 that inferential measures should not be used in the descriptive data. The following sentence is the quote from STROBE: “Inferential measures such as standard errors and confidence intervals should not be used to describe the variability of characteristics, and significance tests should be avoided in descriptive tables. Also, P values are not an appropriate criterion for selecting which confounders to adjust for in analysis; even small differences in a confounder that has a strong effect on the outcome can be important”⁶.

S1.2: Table 2, lines 132-140: It appears that > 20 variables were included in the adjustment model. Contrast this with the counts for stillbirth, infant, neonatal or postnatal mortality among the underwt, and obese cohorts and the likelihood of over fitting the model is high. Given the size of the control group, a matching algorithm should be done to corroborate the associations found.

Response to S1.2: Indeed, this is an important point. However, we used data adaptive machine learning algorithms to fit all models used in our analyses. Cross validation was used to avoid overfitting all models used for these analyses. Several theoretical and simulation studies have demonstrated the optimal performance of the methods we have used, particularly with regards to overfitting^{7,8}.

In terms of the use of a matching algorithm, we admit that we are not quite certain which algorithm(s) the statistical editor is suggesting. If, in fact, by “matching algorithm” is meant an analysis in which pregnancies are matched (e.g., 1:1) on the basis of confounders or the propensity score, we would not expect this approach to yield similar results. Our analysis quantifies a marginally adjusted parameter in the population. On the other hand, a matched analysis quantifies a very different conditionally adjusted parameter. Thus, differences in these results could arguably be due to factors that we are not interested in.

On the other hand, if the statistical editor meant by “matching analysis” some other algorithm that enables us to quantify the same marginal parameter, this would also be unnecessary. In our approach, we used a stacking algorithm to combine 31 different algorithms into a single meta-algorithm (stacked generalization). Given the diverse set of algorithms we used in this analysis that included tree based, bagged algorithms, boosting algorithms, regression algorithms, and others, it is unlikely that an alternative algorithm will yield results that differ greatly from what we currently found.

ASSOCIATE EDITOR'S COMMENTS

In your revision please

AE1.1: Remove causal language

Response to AE1.1: In the current revision, we removed the usage of “effect” in situations where they could possibly be interpreted as a proxy of association. We also changed our title per request of reviewer 2 (see details in response to R2.1). The terms “effect” kept in this revision refers to the parameters we are trying to estimate.

AE1.2: As suggested by reviewer, please corroborate your findings with a matching algorithm.

Response to AE1.2: As mentioned in the statistical reviewer's comment (S1.2), the suggestion of conducting matching algorithm was due to the concern of model overfitting. In our response to S1.2, we explained the reasons why our analytic methods can avoid overfitting. Also, we further explained the matching algorithm may not be an appropriate approach to verify our observed findings.

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