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.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Jul 01, 2019
To: "Lisa M. Bodnar" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1043

RE: Manuscript Number ONG-19-1043

A population-based study of gestational weight gain and adverse birth outcomes in twin pregnancies

Dear Dr. Bodnar:

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 Jul 22, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective review using a large data base from Pennsylvania with the objective of evaluating the association between gestational age weight gain z-scores in twins and SGA< LGA< preterm birth <32 weeks, c-section, and infant death. Objective could benefit from more specificity. Authors do meet the objective as written.

1. Line 48-52 and line 98-100 - objective shoudl be worded the same in both these places and be more specifc

2. Line 68-71 - vague as written

3. Line 82-83 - please add which poor pregnancy and birth outcomes here

4. Methods - pleae move the explanation of z-score to the beginning of this section or to the introductin so the reader knows what it is

5. Line 115-117 - this is subject to women's inaccurate memories

6. Line 126-129 - and 129-131 - references here please

7. Line 136 - reference here and please explain why <32 weeks was used for a preterm birth delivery

8. Line 306-314 - these are weaknesses/limitations of this study. Study only considered pre-existing hypertension and diabetes in women but did not include other pre-existing diseases or any other pregnancy related diseases, including preeclampsia and gestational diabetes as acknolwedged, that can affect maternal weight gain

9. Line 320-332 - conclusions lack a clinical correlation and recommendations for providers

Reviewer #2:

1. Why did the authors limit the study only to live-born twins? It seems as was set up in the introduction, that stillbirth is an important outcome, especially among twins.

2. I think it would be helpful for the authors to presented the adjusted results in addition to the unadjusted results in table 3 or to provide a separate table of the adjusted risk differences in the main results.

3. The observed total weight gain across increasing obesity grades decreased substantially from 16 (9.2), 13 (9.7), and 11 (11) kg. Yet, in table 3, the expected total weight gain at 37 weeks which corresponded to the z-score cutoffs was the same. This doesn't seem to make sense in practice since we know that women with more severe obesity gain less weight across pregnancy.

4. "After adjustment for confounders, the negative association between gestational weight gain and SGA birth was strongest among underweight and normal weight women, and weaker for overweight and obese women (Figure 1, Supplemental Figure 1)." Can the authors be more specific on what the difference is between Figure 1 and Sup. Figure 1?

5. "After adjustment for confounders, the negative association between gestational weight gain and SGA birth was strongest among underweight and normal weight women, and weaker for overweight and obese women (Figure 1, Supplemental Figure 1)." I am not following the authors statement that the negative association between weight gain and SGA was weaker for women with obesity. Looking at the graphs it seems that at higher weight gain for women with normal weight the green line tends to flatten out whereas for women with grade 3 obesity the green line continues to decrease and never plateaus.

6. "However, among obese women, there were only 1.1 (0.7, 1.4) excess cases of SGA, comparing 231 a z-score of -1 SD (6.4 kg at 37 weeks) to 0 SD (14 kg at 37 weeks)." Which grade of obesity are the authors referring to in this sentence?

7. It is difficult to assess from the figures what is statistically and clinically significant. For example, looking at the figure it does not appear that the risk for death changes much with + weight gain z-score. Can the authors come up with an alternative way of showing the results to help the reader with this information- I think this may go back to the comment above regarding an adjusted results table.

8. Line 239: "High gestational weight gain was associated with an increased risk of infant death among underweight, normal weight, and overweight women. For instance, a gestational weight gain zscore of +2 SD (the equivalent of 37 kg at 37 weeks) among normal weight women was associated with 1.3 (95% CI 0.5, 2.2) excess cases of infant death per 100 births compared with a z-score of 0 SD (20 kg at 37 weeks) (Supplemental Table 1)"
Line 277: "Only high gestational weight gain z-scores were associated with infant death among underweight and overweight women"

These two statements by the authors in the results and discussion do not seem to agree with each other.

9. Line 284: "We found that very low weight gain (0.9 to 6.4 kg at 37 weeks) among women with severe obesity increased the risk of SGA birth," Can the authors be specific on the amount of increased risk of SGA birth? These details will likely be important for individuals with obesity and their clinicians in evaluating the risk of SGA, especially as low weight gain does not come with an increased risk for PTB or infant death.

10. I would appreciate if the discussion had more discussion on the biological relevance of weight gain for these outcomes and whether weight gain is actually modifiable for women with twins.

11. I think the discussion would benefit with some commentary on the generalizability of the PENN MOMs cohort to women with twin pregnancies as a whole in the US.

12. Lastly, the authors should edit the manuscript to use people first language when referencing obesity.

Reviewer #3: The authors sought to examine the relationship between gestational weight gain and adverse birth outcomes in twin pregnancies using data from the Pennsylvania linked infant birth and death records from 2003-2013.

The rationale for the study is provided, and the methods are well explained. My concern lies in the presentation of the results. The authors present one figure that has 6 parts and 3 tables as part of the main manuscript. In addition, the authors provide 3 figures and 4 tables as supplemental content. The supplemental content is discussed heavily in the results section, which I found odd. Ideally, the key analyses and findings should be presented within the report as opposed to online supplemental content. I would encourage the authors to consider revisiting their figures and tables and condensing the number of figures and tables provided - and to make sure that the bulk of the results referenced in the paper are cited within the paper's tables. Because of the volume of tables and figures included in this manuscript and the complexity of the analyses, it was difficult at times to follow the authors' argument - especially in the last page of the results section. I personally did not find the figures helpful.

Additional comments:

1. Introduction, references 1 & 4: There are updated data on the number and percentage of twin births in the US, the trend over time, and the percentage preterm. I encourage the authors to consider citing the following report to provide the

latest estimates: https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf.

2. Introduction, references 2 & 3: There are also updated data from the national linked birth and infant death file - https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_09.pdf .

3. Methods, page 7, line 136: The authors state that they defined preterm birth as delivery before 32 weeks' gestation. Technically, the definition of early preterm birth is at less than 34 completed weeks of gestation. So do the authors mean very early preterm birth or are they defining 'early preterm birth' differently because these are twin pregnancies? Clarification is needed, as preterm birth is not less than 32 weeks' gestation.

4. Methods, page 9: The authors discuss the quality of the birth certificate data. The authors may or may not find the following recent publication useful as a complement to their own quality work on the birth certificate: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_08-508.pdf

5. Results, Tables: This is a minor comment, but the percentages should be presented all to one decimal place for consistency and readability.

6. Results (first full page, first paragraph): There is a slight inconsistency in the reporting of some of the estimates in Table 1 - the authors are off by one tenth (3.4 vs. 3.3%, 6.6 vs. 6.7%). Please confirm which are accurate and be consistent in both tables and text.

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: Should format the characteristics as n(%) to give the reader a sense of the absolute numbers in various categories.

2. Tables 2, 3: Some of the subsets have small counts, so the model results shown in Fig 1 are, in some cases, likely unreliable. For example, for underwgt, number of infant deaths and number of LGA, esp outside of ± 1SD are few; For grade 2 and grade 3 obese, the number of infant deaths is also few outside of ± 1SD. The figures for those groups should be removed due to low counts.

Suggest, as on-line material, including a new version of Fig 1 that was organized by PTB, SGA, LGA and infant death, showing the various wgt classes on the same risk vs GA wgt gain z-scale.

Associate Editor's Comments:

Dr. Bodnar (Lisa),

We are very happy that you sent us this work. That said, in its present form, many of our clinical readers will not benefit as much as they might if it were written in a more clinically understandable way. To that end,

1) Please in the abstract, somehow make the Z scores more generally tangible by providing actual weight gain ranges with which they are associated;

2) In your Discussion, please explicitly compare and contrast as appropriate your findings to the weight gain ranges for twins recommended by the IOM and contained in ACOG Committee Opinion 548 "Weight Gain During Pregnancy";

3) The Figure(s) is overwhelming. Rather than put four outcomes in one figure, please instead include only one outcome and compare it across your BMI categories;

4) We are concerned that due to the infrequency of outcomes in the upper weight classes that a statistical and graphical analysis is not supportable and that you consider collapsing the classes

We look forward to a revised manuscript.

Sincerely,
Dwight

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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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. 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.

5. 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, 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).

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

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. 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.

13. 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.

14. 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 via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

15. The Journal's Production Editor had the following to say about this manuscript:

"Figure 1: Please upload as a separate figure file on Editorial Manager. While these figures might be okay, we do prefer to use the original figure file (jpeg, eps, tiff, etc.) as opposed to images pasted into Word. Often these images lose resolution. Supplemental figures are okay since they will remain in Word."

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.

16. 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 http://edmgr.ovid.com/acd/accounts/ifauth.htm.

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.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 22, 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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[redacted]

July 16, 2019

Dr. Dwight Rouse
Associate Editor
Obstetrics & Gynecology

RE: Manuscript Number ONG-19-1043

Dear Dr. Rouse:

Thank you very much for the prompt and high-quality review of our manuscript, "A population-based study of gestational weight gain and adverse birth outcomes in twin pregnancies." We are grateful for the opportunity to revise and resubmit this work. We believe the reviews have helped to substantially strengthen and clarify our paper. We are excited for the opportunity to publish our article in Obstetrics & Gynecology.

As requested, we have provided a point-by-point response to your comments as well as those of the three reviewers and the statistical reviewer. We have marked all changes to the manuscript using "track changes" in Microsoft Word. The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. This manuscript has not been submitted to other journals for publications.

Thank you for considering our revised manuscript. We look forward to your comments.

Sincerely,

Lisa M Bodnar
Professor and Vice-Chair of Research, Department of Epidemiology
University of Pittsburgh Graduate School of Public Health

RE: Manuscript Number ONG-19-1043

A population-based study of gestational weight gain and adverse birth outcomes in twin pregnancies

Associate Editor's Comments:

Dr. Bodnar (Lisa),

We are very happy that you sent us this work. That said, in its present form, many of our clinical readers will not benefit as much as they might if it were written in a more clinically understandable way. To that end,

Please in the abstract, somehow make the Z scores more generally tangible by providing actual weight gain ranges with which they are associated;

Response: We have modified the paper to ensure that wherever possible, we refer to the total gestational weight gain that is equivalent to the z-score at 37 weeks gestation, and include the corresponding z-score in parentheses. We have replaced the z-score x-axis in Figure 2 with total weight gain equivalent at 37 weeks. Please note that we cannot use this same x-axis for Figure 1 because z-scores correspond to different gestational weight gains for normal weight, overweight, and obese women.

The Figure(s) is overwhelming. Rather than put four outcomes in one figure, please instead include only one outcome and compare it across your BMI categories;

Response: We spent a long time exploring options for presenting the data in this figure. We have added the figure you request (now Figure 1), which shows one outcome in each panel. We agree that this presentation allows an easy comparison across BMI categories. Table 4 presents the risk differences that directly correspond to this figure. Nevertheless, we opted to keep our original figure with all outcomes on one panel shown separately for each BMI category (now Figure 2). Figures like this allow the reader to examine the trade-offs in risk with increasing or decreasing gestational weight gain. Indeed, the IOM Committee used figures like this when determining its current recommendations. To make this figure more interpretable, we (1) added vertical lines reflecting the IOM recommended weight gain ranges for each BMI group; (2) changed the x-axis to reflect equivalent total weight gain at 37 weeks; and (3) added a color-coded legend for each outcome. We have interpreted this figure in the Results relative to the IOM guidelines, which addresses your point below. We hope you agree that this change has substantially improved the readability and interpretability of our findings for the audience.

Change to manuscript: We have added a new Figure 1 to the paper that shows associations between gestational weight gain and adverse outcomes with all BMI categories on the same panel. We have labeled each BMI group on the figure for greater interpretability. We have changed the original figure (now Figure 2) to include vertical lines indicating the IOM recommended range. The Results paragraph 5 interprets these findings relative to the IOM guidelines.

In your Discussion, please explicitly compare and contrast as appropriate your findings to the weight gain ranges for twins recommended by the IOM and contained in ACOG Committee Opinion 548 "Weight Gain During Pregnancy";

Response: In addition to the changes to Figure 2 to include the IOM-recommended range, we have added text to the Results and Discussion comparing and contrasting our findings to these guidelines as well.

Change to manuscript: Results, 5th paragraph: "Figure 2 shows associations between pregnancy weight gain and risk of outcomes simultaneously for women in each BMI category (grade 2 and 3 obesity are combined in Supplemental Figure 1). We overlaid the 2009 IOM provisional recommended total weight gain ranges for twins with vertical lines (underweight – no recommendation; normal weight 16.8–24.5 kg; overweight 14.1–22.7 kg; obese 11.3–19.1 kg). Within the IOM-recommended weight gain ranges for normal weight, overweight, and grade 1 obese women, there were meaningful declines in SGA risk and increases in LGA risk. Below the guidelines, risks of SGA, infant death (for normal weight women only), and early preterm birth were elevated. At the upper limit of the IOM recommendations for these 3 BMI groups, the risk of SGA and LGA were approximately 10%, but weight gains greater than the upper cut-point were associated with increasing risk of preterm birth, infant death, and cesarean delivery. For women with severe obesity, weight gain below the provisional guidelines was associated with an elevated risk of SGA (adjusted predicted probabilities >12%), but not preterm birth or infant death. At gains higher than recommended, risk of LGA increased sharply. In sum, most excess risk was observed at weight gains more than 1 SD away from the mean: <14 kg or >27 kg in underweight or normal weight women, <11 kg or >28 kg in overweight women, and <6.4 kg or >26 kg in women with obesity."

Discussion, last paragraph: "Our study, which is the largest to-date on maternal weight gain in twin pregnancies, provides evidence that women should avoid weight gain well above or well below the IOM provisional guidelines: <14 kg or >27 kg in underweight or normal weight women, <11 kg or >28 kg in overweight women, and <6.4 kg or >26 kg in women with obesity. Nearly 1 in 3 women gains outside these ranges. More precise evidence-based weight gain ranges that optimize health outcomes are needed, but require additional data. Research is needed on the relation between pregnancy weight gain z-scores in twin gestations and a wide range of additional health outcomes, including preeclampsia, gestational diabetes, stillbirth,

maternal postpartum weight retention, childhood obesity, child cognition, and longer-term health. To balance maternal and child health risks, policy makers require data that quantify the relative seriousness of these health outcomes, as determined by women and their health care providers. Filling these critical knowledge gaps will help lead to guidelines that balance risks of high and low gain for the short- and long-term health of women and their twins, and guide medical practice and public health policies aimed at improving maternal and child outcomes for twin pregnancies."

We are concerned that due to the infrequency of outcomes in the upper weight classes that a statistical and graphical analysis is not supportable and that you consider collapsing the classes

Response: We appreciate this concern. We have addressed it by presenting results for grade 2 and 3 obesity combined in Table 4 as well as Supplemental Figure 1. We did not remove the results for grade 2 obesity and grade 3 obesity because the figures model gestational weight gain as a continuous variable, which allows for greater statistical power than what is observed in the categorical analyses of Table 3. The confidence intervals shown in the tables and figures reflect the imprecision, and we do not over-interpret these findings. Further, the Institute of Medicine Committee to Reevaluate Weight Gain Guidelines issued a call for research on weight gain related to a range of health outcomes separately according to BMI group. In particular, they were especially interested in data that may inform whether weight gain guidelines should vary according to grade of obesity. Given the complete lack of information in the literature on severely obese women with twin pregnancies, we feel the estimates we show have value. These data can be used in future meta-analyses.

Change to manuscript: Table 4 and Supplemental Figure 1 show data combined for grade 2 and 3 obesity.

REVIEWER COMMENTS:

Reviewer #1: This is a retrospective review using a large data base from Pennsylvania with the objective of evaluating the association between gestational age weight gain z-scores in twins and SGA< LGA< preterm birth <32 weeks, c-section, and infant death. Objective could benefit from more specificity. Authors do meet the objective as written.

Response: Thank you for this comment. We have clarified the objective.

Change to the paper: Introduction, last paragraph. The objective now reads, "Our objective was to evaluate the association between gestational weight gain and small- and large-for-gestational-age birth (SGA, LGA), early preterm birth <32 weeks, cesarean delivery, and infant death separately by prepregnancy BMI category in a large, population-based cohort of twin births."

1. Line 48-52 and line 98-100 - objective should be worded the same in both these places and be more specific.

Response: As noted above, we have modified the objective to be explicit in the Abstract and Introduction.

Change to manuscript: Introduction, last paragraph. The objective reads, "Our objective was to evaluate the association between gestational weight gain and small- and large-for-gestational-age birth (SGA, LGA), early preterm birth <32 weeks, cesarean delivery, and infant death separately by prepregnancy BMI category in a large, population-based cohort of twin births."

2. Line 68-71 - vague as written

Response: We have modified the conclusions of the Abstract.

Change to manuscript: Abstract, Conclusion, "Our study, which is the largest to-date on maternal weight gain in twin pregnancies, suggests that women should avoid very low or very high weight gains: <14 kg or >27 kg in underweight or normal weight women, <11 kg or >28 kg in overweight women, and <6.4 kg or >26 kg in women with obesity. More refined evidence-based recommendations require data on additional health outcomes and on the relative seriousness of each outcome."

3. Line 82-83 - please add which poor pregnancy and birth outcomes here

Response: We added a list of poor pregnancy and birth outcomes, but the paper was over the required word count, so we ultimately removed this.

4. Methods - please move the explanation of z-score to the beginning of this section or to the introduction so the reader knows what it is

Response: We have moved the brief description of z-scores to the objective in the Introduction.

Change to manuscript: Introduction, last paragraph, last line. Insertion of the sentence "Gestational weight gain z-scores are a continuous measure of weight gain that are standardized for gestational age."

5. Line 115-117 - this is subject to women's inaccurate memories

Response: We agree that there is a potential for maternal prepregnancy weight and height to be misreported. We undertook a validation substudy within the cohort to determine the extent

of misclassification and its impact on the reported associations (last paragraph of Methods and last paragraph of Results).

6. Line 126-129 - and 129-131 - references here please

Response: We have added two references describing the z-scores.

Change to manuscript: Methods, 2nd paragraph. Insertion of the following references:
Hutcheon, J. A., et al. (2012). "The bias in current measures of gestational weight gain." Paediatric and Perinatal Epidemiology 26: 109-116.
Hutcheon, J. A. and L. M. Bodnar (2018). "Good Practices for Observational Studies of Maternal Weight and Weight Gain in Pregnancy." Paediatr Perinat Epidemiol 32(2): 152-160.

7. Line 136 - reference here and please explain why <32 weeks was used for a preterm birth delivery

Response: We now refer to this as "early preterm birth <32 weeks" throughout the manuscript. We selected this cut-point because the vast majority of the neonatal morbidity in twins occurs at <32 weeks. Therefore, this outcome is of particular interest.

Change to manuscript: Methods, 3rd paragraph. "We defined early preterm birth as delivery before 32 weeks' gestation. We chose this cut-off because the risk of neonatal morbidity is highest at <32 weeks (19)."

8. Line 306-314 - these are weaknesses/limitations of this study. Study only considered pre-existing hypertension and diabetes in women but did not include other pre-existing diseases or any other pregnancy related diseases, including preeclampsia and gestational diabetes as acknowledged, that can affect maternal weight gain

Response: We adjusted for pre-existing hypertension and diabetes in our analysis. We considered preeclampsia and gestational diabetes, but opted not to include them as covariates in models because they likely lie on the causal pathway from gestational weight gain to adverse outcomes we studied. Therefore, they do not meet the definition of a confounder of the associations we studied. We have added this to the Discussion.

Change to manuscript: Discussion, 7th paragraph. We added, "We also did not adjust for these pregnancy complications because they likely lie on the causal pathway, and therefore do not meet the definition of a confounder (56)."

9. Line 320-332 - conclusions lack a clinical correlation and recommendations for providers

Response: We have substantially altered the paper to compare our findings to the IOM provisional guidelines.

Change to manuscript: Discussion, last paragraph. Insertion of "Women with twin gestations should avoid weight gain well above or well below the IOM provisional guidelines: <14 kg or >27 kg in underweight or normal weight women, <11 kg or >28 kg in overweight women, and <6.4 kg or >26 kg in women with obesity."

Reviewer #2:

1. Why did the authors limit the study only to live-born twins? It seems as was set up in the introduction, that stillbirth is an important outcome, especially among twins.

Response: We agree that stillbirth is an important outcome to consider for twin pregnancies. However, including it in our study would have been problematic. Rigorously exploring the relation between gestational weight gain and stillbirth requires data on the timing of the fetal death and the last measured antenatal weight while the fetus was last known to be alive. If the fetus died several weeks before delivery, data on total weight gain at delivery and the gestational age at delivery (the only two variables available in the vital records) will lead to inaccurate measures of the exposure of interest, and lead to spurious findings.

2. I think it would be helpful for the authors to present the adjusted results in addition to the unadjusted results in table 3 or to provide a separate table of the adjusted risk differences in the main results.

Response: Thank you for this suggestion. Reviewer #3 has also noted below that we rely heavily on discussion Supplemental Table 1 in our results, which show the adjusted risk differences. Therefore, we have made this Table 4 of our revised manuscript.

Change to manuscript: Supplemental Table 1 has been moved into the manuscript as Table 4. This table shows the adjusted risk differences for weight gain z-scores and each adverse outcome according to prepregnancy BMI category.

3. The observed total weight gain across increasing obesity grades decreased substantially from 16 (9.2), 13 (9.7), and 11 (11) kg. Yet, in table 3, the expected total weight gain at 37 weeks which corresponded to the z-score cutoffs was the same. This doesn't seem to make sense in practice since we know that women with more severe obesity gain less weight across pregnancy.

Response: We converted the z-scores in Table 3 to the equivalent total weight gain at 37 weeks. Women in all grades of obesity have the same ranges because there is one z-score chart for all obese women. We have added a footnote to this table explaining this.

Change to manuscript: Table 3 footnote now reads, "Gestational weight gain z-scores <-1, -1 to +1, and >+1 SD correspond to total gestational weight gains at 37 weeks gestation. Total weight gain ranges are the same for all grades of obesity because there is one z-score chart for obese women (BMI ≥30 kg/m^2)."

4. "After adjustment for confounders, the negative association between gestational weight gain and SGA birth was strongest among underweight and normal weight women, and weaker for overweight and obese women (Figure 1, Supplemental Figure 1)." Can the authors be more specific on what the difference is between Figure 1 and Sup. Figure 1?

Response: Supplemental Figure 1 showed the associations between weight gain z-scores and each outcome among underweight women. It differed from the figure that appeared in the paper because it showed an extended range of the y-axis in order to capture the high risks of SGA birth. In the revised paper, we have removed this figure.

Change to manuscript: We have removed the original Supplemental Figure 1.

5. "After adjustment for confounders, the negative association between gestational weight gain and SGA birth was strongest among underweight and normal weight women, and weaker for overweight and obese women (Figure 1, Supplemental Figure 1)." I am not following the authors statement that the negative association between weight gain and SGA was weaker for women with obesity. Looking at the graphs it seems that at higher weight gain for women with normal weight the green line tends to flatten out whereas for women with grade 3 obesity the green line continues to decrease and never plateaus.

Response: We agree that this statement was confusing. We have substantially rewritten the Results section describing the new Figure 1, Table 4, and Figure 2 for clarity. The statement has been removed from the paper.

6. "However, among obese women, there were only 1.1 (0.7, 1.4) excess cases of SGA, comparing a z-score of -1 SD (6.4 kg at 37 weeks) to 0 SD (14 kg at 37 weeks)." Which grade of obesity are the authors referring to in this sentence?

Response: This sentence is referring to grade 1 obesity. However, in our revised text, this statement has been removed.

7. It is difficult to assess from the figures what is statistically and clinically significant. For example, looking at the figure it does not appear that the risk for death changes much with + weight gain z-score. Can the authors come up with an alternative way of showing the results to help the reader with this information- I think this may go back to the comment above regarding an adjusted results table.

Response: Our addition of Table 4 to the manuscript with the adjusted risk differences will allow readers to determine quantitative differences in risk rather than relying on the exclusively on the figures. Further, we have added a new figure (Figure 1) that shows these curvilinear associations between gestational weight gain and each outcome by BMI category

Change to manuscript: We have added Table 4 to the manuscript with adjusted risk differences for a range of gestational weight gain z-scores. Revise Figure 1 also illustrates these associations.

8. Line 239: "High gestational weight gain was associated with an increased risk of infant death among underweight, normal weight, and overweight women. For instance, a gestational weight gain zscore of +2 SD (the equivalent of 37 kg at 37 weeks) among normal weight women was associated with 1.3 (95% CI 0.5, 2.2) excess cases of infant death per 100 births compared with a z-score of 0 SD (20 kg at 37 weeks) (Supplemental Table 1)."
Line 277: "Only high gestational weight gain z-scores were associated with infant death among underweight and overweight women".
These two statements by the authors in the results and discussion do not seem to agree with each other.

Response: Thank you for pointing out this confusing text. We have revised the text in the Discussion to be consistent with the results.

Change to manuscript: Discussion, 4th paragraph. "In our study, gestational weight gain z-score had a U-shaped association with preterm birth <32 weeks among women without obesity. Risk of infant death was elevated with high gestational weight gain among women without obesity and low weight gain only among normal weight women."

9. Line 284: "We found that very low weight gain (0.9 to 6.4 kg at 37 weeks) among women with severe obesity increased the risk of SGA birth," Can the authors be specific on the amount of increased risk of SGA birth? These details will likely be important for individuals with obesity and their clinicians in evaluating the risk of SGA, especially as low weight gain does not come with an increased risk for PTB or infant death.

Response: We have revised our results text substantially. We updated the current text to include the increased risk of SGA, as requested.

Change to manuscript: Results, 6th paragraph. Inserted, "For women with severe obesity, weight gain below the provisional guidelines was associated with an elevated risk of SGA (adjusted predicted probabilities >12%), but not preterm birth or infant death."

10. I would appreciate if the discussion had more discussion on the biological relevance of weight gain for these outcomes and whether weight gain is actually modifiable for women with twins.

Response: Very little is known about the modifiability of gestational weight gain in women with twin pregnancies, the causal nature of these relationships to one another, or the biological underpinnings of the associations. We have revised our Discussion to reflect this.

Change to manuscript: Discussion, 8th paragraph. Insertion of: "Lifestyle interventions can modify gestational weight gain and improve some outcomes in singleton pregnancies (58-61). While some evidence suggests that women with twin gestations who agree to participate in a dietary intervention program are more likely than non-participants to meet maternal weight gain goals (62, 63), randomized trials have not tested whether interventions in twin pregnancies can modify maternal weight gain and adverse outcomes. As a result, the causality and the biological basis of associations between pregnancy weight gain and outcomes in twin gestations are unknown."

11. I think the discussion would benefit with some commentary on the generalizability of the PENN MOMs cohort to women with twin pregnancies as a whole in the US.

Response: Thank you. We now comment on the generalizability of our findings to US twin pregnancies.

Change to manuscript: Discussion, 7th paragraph, inserted, "In the study period, twin birth rates and the distribution of maternal age and race/ethnicity in twin births were similar between Pennsylvania and the U.S., which lends support to the generalizability of our findings."

12. Lastly, the authors should edit the manuscript to use people first language when referencing obesity.

Response: Thank you for this important reminder. We have changed all language to person-first language in reference to obesity.

Change to manuscript: We have made 8 changes to person-first language in reference to obesity throughout the manuscript.

Reviewer #3:
The authors sought to examine the relationship between gestational weight gain and adverse birth outcomes in twin pregnancies using data from the Pennsylvania linked infant birth and death records from 2003-2013.

The rationale for the study is provided, and the methods are well explained. My concern lies in the presentation of the results. The authors present one figure that has 6 parts and 3 tables as part of the main manuscript. In addition, the authors provide 3 figures and 4 tables as supplemental content. The supplemental content is discussed heavily in the results section, which I found odd. Ideally, the key analyses and findings should be presented within the report as opposed to online supplemental content. I would encourage the authors to consider revisiting their figures and tables and condensing the number of figures and tables provided - and to make sure that the bulk of the results referenced in the paper are cited within the paper's tables. Because of the volume of tables and figures included in this manuscript and the complexity of the analyses, it was difficult at times to follow the authors' argument - especially in the last page of the results section. I personally did not find the figures helpful.

Response: Thank you for this insight. We agree and have substantially altered the tables and figures in response. We relied on results from Supplemental Table 1 in the text and have now moved this to Table 4 of the paper. We have also changed Figure 1 (now Figure 2) to make it more interpretable for the journal's readership, as recommended by the editor and the statistical editor. We have also added a figure (Figure 1) that allows for easier comparison of associations across BMI groups.

Change to manuscript: Supplemental Table 1 now appears as Table 4. Figure 1 now shows the curvilinear associations between weight gain and each adverse outcome with all BMI groups shown on each outcome panel. Figure 2 now shows the simultaneous associations between weight gain and each outcome shown with each BMI groups on a separate panel. We have made this figure easier to interpret by changing the x-axis to total weight gain equivalent to z-scores and vertical lines indicating the IOM recommended ranges overlaid on the curves. The text of the Results has been substantially rewritten to reflect these changes and to improve clarity.

1. Introduction, references 1 & 4: There are updated data on the number and percentage of twin births in the US, the trend over time, and the percentage preterm. I encourage the authors to consider citing the following report to provide the latest estimates: https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf

Response: Thank you very much for this suggestion. We have updated the statistics and citations on twin births in the U.S. in the introduction.

Change to manuscript: Introduction, 1st paragraph. We now state, "Over the past 40 years, the number of twins born in the U.S. more than doubled" and "While twins make up 3.3% of all births, they account for over 20% of the burden of preterm births."

2. Introduction, references 2 & 3: There are also updated data from the national linked birth and infant death file https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_09.pdf

Response: We thank the reviewer again for this recommendation. We have updated the introduction with the latest statistics.

Change to manuscript: Introduction, 1st paragraph. "Compared with singletons, twins are 2.5almost three times as likely to die in utero (2) and are more than four times as likely to die in the first month year of life (4)."

3. Methods, page 7, line 136: The authors state that they defined preterm birth as delivery before 32 weeks' gestation. Technically, the definition of early preterm birth is at less than 34 completed weeks of gestation. So do the authors mean very early preterm birth or are they defining 'early preterm birth' differently because these are twin pregnancies? Clarification is needed, as preterm birth is not less than 32 weeks' gestation.

Response: As noted above, we have revised the manuscript to refer to this outcome as "early preterm birth <32 weeks."

Change to manuscript: Methods, 3rd paragraph. "We defined early preterm birth as delivery before 32 weeks' gestation. We chose this cut-off because the risk of neonatal morbidity is highest at <32 weeks (19)."

4. Methods, page 9: The authors discuss the quality of the birth certificate data. The authors may or may not find the following recent publication useful as a complement to their own quality work on the birth certificate: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_08-508.pdf

Response: This citation refers to a manuscript that validated a number of the "checkbox" items on the U.S. birth certificate. Unfortunately, the items validated were not any of the primary exposures or outcomes of our study, so we opted not to cite it in this paper.

5. Results, Tables: This is a minor comment, but the percentages should be presented all to one decimal place for consistency and readability.

Response: When measurements are added, subtracted, multiplied or divided, the answer can contain no more significant figures than the least accurate measurement. So, to report a

percentage to nn.n% significant digits, both the numerator and the denominator have to be informed by more than 100 people for every calculation that enters into the sum to 100%. That condition does not hold in our large study, so we have reported all results to two significant figures (nn%, n.n%, 0.nn%).

Change to manuscript: none

6. Results (first full page, first paragraph): There is a slight inconsistency in the reporting of some of the estimates in Table 1 - the authors are off by one tenth (3.4 vs. 3.3%, 6.6 vs. 6.7%). Please confirm which are accurate and be consistent in both tables and text.

Response: The estimates may not total 100% due to rounding and the use of two significant figures, as noted above. We have added a footnote in Table 1 to reflect this.

Change to manuscript: Table 1, footnote now reads, "Figures may not add to 100% due to rounding."

STATISTICAL EDITOR'S COMMENTS:

1. Table 1: Should format the characteristics as n(%) to give the reader a sense of the absolute numbers in various categories.

Response: We have made this change.

Change to manuscript: Table 1 presents n (%) for all categorical characteristics.

2. Tables 2, 3: Some of the subsets have small counts, so the model results shown in Fig 1 are, in some cases, likely unreliable. For example, for underwgt, number of infant deaths and number of LGA, esp outside of ± 1SD are few; For grade 2 and grade 3 obese, the number of infant deaths is also few outside of ± 1SD. The figures for those groups should be removed due to low counts.

Response: There are fewer than 20 cases of infant death in one of the extreme weight gain groups for underweight and grade 3 obese women. The confidence intervals shown in the tables and figures reflect the imprecision, and we do not over-interpret the point estimates. Further, the Institute of Medicine Committee to Reevaluate Weight Gain Guidelines issued a call for research on a range of health outcomes separately according to BMI group. In particular, they were especially interested in data that may inform whether weight gain guidelines should vary according to grade of obesity. Given the complete lack of information in the literature on severely obese women with twin pregnancies, we feel the estimates we show have value. We also note that the figures model gestational weight gain as a continuous variable, which allows for greater statistical power than what is observed in the categorical analyses of Table 3. We

have added analyses to our paper that combine grades 2 and 3 obesity because their associations with weight gain were not meaningfully different. However, we also prefer to present the results separately for grade 2 and 3 obese women so these data can be used in future meta-analyses.

Change to manuscript: Table 4 and Supplemental Figure 1 show data combined for grade 2 and 3 obesity.

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.

Response: OPT-IN (A)

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.

Response: We used state vital records for this analysis. We have noted throughout the Materials and Methods section the validity (tested empirically) of the key variables we employed in this analysis.

5. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

Response: We have ensured that our paper does not exceed 22 pages (minus 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).*

Response: We acknowledge that we understand this policy.

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

Response: This has been added.

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."

Response: This has been added.

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.

Response: This has been checked. The word count is 297.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://nam05.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Fabbreviations.pdf&data=02%7C01%7Cbodnar%40edc.pitt.edu%7Cee4621a60a214ba0cff108d6fe59a6d4%7C9ef9f489e0a04eeb87cc3a526112fd0d%7C1%7C1%7C636976058343693460&sdata=YUNadGGoMuR7pCRb%2BWK%2Bhym5feMX2y1uC4w2gHi30Zg%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 have confirmed our abbreviations meet the standards.

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.

Response: We have removed the virgule symbol in sentences with words.

12. 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.

Response: We do not include first reports claims.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: https://nam05.safelinks.protection.outlook.com/?url=http%3A%2F%2Fedmgr.ovid.com%2Fong%2Faccounts%2Ftable_checklist.pdf&data=02%7C01%7Cbodnar%40edc.pitt.edu%7Cee4621a60a214ba0cff108d6fe59a6d4%7C9ef9f489e0a04eeb87cc3a526112fd0d%7C1%7C1%7C636976058343693460&sdata=m8cdX3h3YC8ZXe1irvlj8mjWP1z5TT7sxuau0eM0r0A%3D&reserved=0.

Response: We have confirmed this.

14. 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 via the Clinical Guidance & Publications page at https://nam05.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.acog.org%2FClinical-Guidance-and-Publications%2FSearch-Clinical-Guidance&data=02%7C01%7Cbodnar%40edc.pitt.edu%7Cee4621a60a214ba0cff108d6fe59a6d4%7C9ef9f489e0a04eeb87cc3a526112fd0d%7C1%7C1%7C636976058343693460&sdata=lcwSB9OlxEQlfW4N%2Bv6ehtWkDTRKHXafOxeLQiidSo4%3D&reserved=0.

Response: We have confirmed this.

15. The Journal's Production Editor had the following to say about this manuscript:

"Figure 1: Please upload as a separate figure file on Editorial Manager. While these figures might be okay, we do prefer to use the original figure file (jpeg, eps, tiff, etc.) as opposed to images pasted into Word. Often these images lose resolution. Supplemental figures are okay since they will remain in Word."

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.

Response: We have uploaded the figure separately.