Author’s response to reviews

Title: The Association between Gestational Weight Gain Z-Score and Stillbirth: A Case-Control Study

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Author’s response to reviews:

Dear Dr. Aronin, Dr. Bodnar, Dr. Himes, and Editorial Staff,

We thank you for the opportunity to revise our manuscript, “The Association between Gestational Weight Gain Z-score and Stillbirth: A Case-Control Study.” We greatly appreciate the constructive comments from both reviewers, and we made considerable revisions to our paper based on your reviews. We are confident that our revised manuscript is significantly stronger thanks to your thoughtful advice. In addition, we appreciate the patience of the editorial staff as we addressed the reviewer comments.
Each of the reviewer comments, along with our response, can be found below. In addition, changes are tracked in the main manuscript file. We also attached a “clean” version of the manuscript file (with all changes accepted) in order to ease readability. We revised all figures and supplementary files.

Thank you again for the opportunity to revise our manuscript. We are happy to respond to any additional inquiries and look forward to your comments.

Many thanks,
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Responses to reviewer comments:

"Lisa Bodnar (Reviewer 1): This manuscript describes a secondary data analysis of the SCRN (Stillbirth Collaborative Research Network) case-control study that seeks to understand the role of gestational weight gain in the etiology of stillbirth at 20 weeks or more. The authors found that low gestational weight gain z-score (a measure of weight gain that is standardized for gestational age) is associated with an increased risk of stillbirth. There is a need for high-quality research exploring this research question, especially to inform future evidence-based gestational weight gain guidelines. I have several major concerns about the manuscript:

Major concerns:

1. Reviewer comment: "The authors evaluate total gestational weight gain at delivery with stillbirth risk, but very minimally address the serious problem of reverse causality (that the death of the fetus reduces subsequent gestational weight gain). They perform a sensitivity analysis limiting the exposure measure to weight gain at the last prenatal visit, but this doesn't capture weight gain before the fetal death (or perhaps it does if the measurement occurs while the fetus was still alive, but the authors do not explore this). This is a serious limitation because this bias would inevitably lead to lower total weight gain among pregnancies that end up with a fetal death, which is what the authors report."
Our response: Thank you for your thoughtful comment. We agree that this is an important issue, and the following sensitivity analyses address this potential limitation:

1. We added a new sensitivity analysis where we restricted to stillbirths who were estimated* to have died ≤1 day before delivery (this analysis had n=342 stillbirths). Results were comparable to main analyses; please see Additional File 5. As a comparison, we also ran models restricted to the minority of stillbirths who were estimated* to have died &gt;1 day before delivery (Additional File 5). Overall trends for z-scores &lt;0 were similar to main analyses after restricting to stillbirths estimated to have died &gt;1 day before delivery, although point estimates were slightly further from the null. In contrast, point estimates for GWG z-scores &gt;0 were closer to the null in models restricted to stillbirths estimated to have died &gt;1 day before delivery.

Note: The average time interval between estimated fetal death and delivery was 1 day in SCRN; the median time interval was only 0.3 days.

2. In another new sensitivity analysis, we re-calculated GWG z-scores for stillbirths using weight and gestational age at last prenatal visit. This analysis was restricted to stillbirths estimated to have been alive at their last prenatal visit (according to the SCRN gestational age at death algorithm). This sensitivity analysis is imperfect, as it does not capture GWG between the last prenatal visit and fetal death (the mean time interval between last prenatal visit and fetal death for stillbirths in this sensitivity analysis was 2.5 (SD 3.2) weeks). Overall trends between GWG z-score and stillbirths were similar in this analysis, but associations between low GWG z-score and stillbirth were attenuated somewhat. Furthermore, high GWG z-score was associated with increased odds of stillbirth.

3. In a third sensitivity analysis, we excluded macerated stillbirths whose weight may have changed between death and delivery. Results from this sensitivity analysis were also comparable to main analyses.

Based on results of these sensitivity analyses, we believe the potential bias due to reverse causality is likely limited in our study.
Gestational age at death was estimated via a SCRN algorithm that used fetal foot length and other measures (Conway et al., Paedr Perin Epid, 2013).

2. Reviewer comment: "A major advantage of the SCRN data is the rigorous phenotyping of stillbirth cause. Evaluating gestational weight gain relative to cause-specific stillbirth would be an important contribution to the knowledge base, but the authors do not explore this. Further, they do not separate stillbirths according to early or late stillbirths, which is another way of looking at different etiologies of stillbirth."

Our response: Thank you for this valuable idea. The revised manuscript includes several sensitivity analyses that address this suggestion. We added sensitivity analyses separating early stillbirths (<28 weeks) from late stillbirths (≥28 weeks), as well as analyses separating preterm stillbirths (<37 weeks) from term stillbirths (≥37 weeks). We also analyzed intrapartum stillbirths separately from non-anomalous antepartum stillbirths.

Finally, we added some preliminary analyses for cause-of-death groupings and stillbirth. We chose 3 cause-of-death groupings which could biologically be associated with GWG and stillbirth and for which we had adequate sample size: 1) placental abnormalities (e.g., uteroplacental insufficiency, maternal vascular conditions, etc.), 2) maternal medical conditions other than hypertension (e.g., diabetes, antiphospholipid syndrome, thyroid disorder, etc.), and 3) obstetric complications during pregnancy (e.g., placental abruption; complications of multiple gestations; the combination of preterm labor, preterm premature rupture of membranes, and cervical insufficiency, etc.).

We view the 3 cause-of-death analyses as preliminary/hypothesis-generating for 2 reasons:

1. We were unable to analyze certain causes of death (e.g., hypertensive disorders) for which we lacked sample size.

2. Causes of fetal death were classified as probable causes, possible causes, or present conditions. We analyzed all stillbirths with probable causes, possible causes, or present conditions related to these three causes. Sample sizes of stillbirths with “probable” or “possible” causes of death were inadequate to allow us to analyze those separately.
3. Reviewer comment: "The literature review is incomplete. At least one methodologically-advanced paper is in the literature on gestational weight gain and stillbirth that is not cited. This paper provides a strong approach that addresses many of the limitation of the current analysis. Although the present paper may not be able to use the same approach, it will guide the authors in a more nuanced approach to their own paper."

Our response: Thank you for pointing out the newer studies on GWG and stillbirth. We added the new paper on GWG and stillbirth to our literature review and cited the strengths of this approach in our discussion section. We also added the recent GWG z-score charts derived from other populations to our literature review. Finally, we added information about the mean gestational age at delivery (and mean gestational age at fetal death, for stillbirths) to the beginning of the results section to increase transparency.

4. Reviewer comment: "The authors apply two different gestational weight gain z-score charts to their data. However, the mean z-score using the normal weight woman standard only was well above 0 SD, which suggests a suboptimal fit. The authors should explore other analytic approaches to determine the appropriateness of the charts to their data. I don't agree with their conclusions in lines 282-285 that the findings are robust to the choice of standard. The higher risk associated with excessive weight gain is unique to the FGLS standard."

Our response: We decided to remove the Intergrowth (FGLS) z-score standard from our paper because the Intergrowth charts were only available for normal weight women and for singleton pregnancies. Furthermore, the Hutcheon et al. z-score charts fit our data better than the Intergrowth charts. For instance, the mean and median z-scores in normal weight women with live births were −0.2 and −0.17, respectively, using Hutcheon et al.’s charts (SD= 0.96). In contrast, the mean and median z-scores in normal weight women were 0.37 and 0.42, respectively, using the Intergrowth charts (SD=1.14).

5. Reviewer comment: "Confounders included in the final model are not listed in the text. This is a major omission."

Our response: Thank you for pointing this out. We listed the confounders in the main text of the revised manuscript.
Minor concerns:

1. Reviewer comment: "The rationale for excluding underweight women, women with preexisting diabetes, and women delivering twins. Gestational weight gain z-scores exist for all of these groups (even twins), and the exclusion of women with diabetes but not hypertension before conception is unjustified."

   Our response: Thank you for your comment. We added in women with preexisting diabetes, underweight women, and dichorionic/diamnionic twins to the study sample. In our revised models, we used generalized estimating equations that accounted for correlation between multiple gestations. We had to combine a few covariate categories in order to attain model convergence; please see Table 1 for the revised categories.

2. Reviewer comment: "Measures of variance of gestational weight gain (absolute gain and z-scores) should be shown in the abstract, tables, and all results text."

   Our response: We added measures of variance (i.e., SDs) of total gestational weight gain and gestational weight gain z-score to the abstract, tables, and all results text.

3. Reviewer comment: "Line 100 in the introduction is redundant with the earlier statement about overweight and obesity, and is unclear why it's needed."

   Our response: Thank you for pointing this out; we removed this sentence.

4. Reviewer comment: "The 4 studies the authors cite on gestational weight gain and stillbirth should be cited directly in the introduction, not the systematic review."

   Our response: We removed the systematic review reference and cited the 4 original studies instead.
5. Reviewer comment: "It is more appropriate to state that the IOM committee to reevaluate gestational weight gain guidelines committee asked for research with stillbirth as the major endpoint."

Our response: Thank you; we added the following sentence to the introduction: “The 2009 Institute of Medicine (IOM) Committee to Reexamine Pregnancy Weight Guidelines requested research on gestational weight gain with stillbirth as a major endpoint.”

6. Reviewer comment: "Lines 113-114 should be referenced."

Our response: Thank you; we added citations for these sentences.

7. Reviewer comment: "The introduction should be shortened."

Our response: We shortened the introduction section.

8. Reviewer comment: "The text on the exposure measure should be shortened. Z-scores are intuitive to calculate."

Our response: Thank you for your comment. We shortened the text describing the exposure measure while maintaining clarity. We balanced your comment with that of the other reviewer, who commented that “The authors have done a nice job making z scores accessible as they are not always intuitive.”

9. Reviewer comment: "P-values should be removed from Table 1. Significance testing is not appropriate. Please see the recent American Statistical Association statement on the use of p-values."

Our response: Thank you; we removed p-values from Table 1/the paper.
10. Reviewer comment: "The sensitivity analyses require n's for the reader to evaluate the appropriateness and value of the approaches and results."

Our response: We added a table with the sample sizes of sensitivity analyses; please see Additional File 3.

11. Reviewer comment: "The mean gestational age is needed to be presented along with the mean gestational weight gain for cases and controls. I imagine these are very different and should be presented for the reader to evaluate weight gain appropriately."

Our response: We added the mean gestational age by case/control status to the text and Table 2.

12. Reviewer comment: "Table 3 does not present results and should be eliminated. These values should be presented as a footnote to relevant tables or figures."

Our response: We deleted this table and added these values as footnotes to relevant tables/figures.

13. Reviewer comment: "The z-scores are shown as 40-week equivalents, and results are interpreted in this regard. However, the vast majority of stillbirths do not deliver at term. Therefore, this is not helpful."

Our response: Thank you for this comment. We removed the references to 40-week equivalents, except for the footnotes noted in comment #12 above.
14. Reviewer comment: "The evaluation of effect modification on the multiplicative scale (rather than the additive scale) is not justified."

Our response: We removed tests for multiplicative interaction.

15. Reviewer comment: "The major exposure based on weight and height, but lines 137-138 do not make it explicit where these variables are ascertained from. It is just stated "medical records and the maternal interview". If maternal interview, when did the interview occur? Were these self-reported or measured?"

Our response: Thank you for your comment. We added the following text to the methods section: “Data collection of consenting women included medical record abstraction, placental pathology, fetal autopsy, and postpartum maternal interview [21]. Most interviews were completed face-to-face before hospital delivery discharge; a few interviews were completed by telephone or other method within 4 weeks of delivery. Sociodemographic information was derived from the maternal interview. Maternal height, pre-pregnancy weight, weight at last prenatal visit, and weight at delivery were abstracted from medical records. If maternal height or pre-pregnancy weight were unavailable in the medical record, women’s self-reported height and pre-pregnancy weight data were taken from the maternal postpartum interview. Self-reported height and pre-pregnancy weight were used for only n=1 observation in our analysis.”

16. Reviewer comment: "Z-scores, if appropriate for the population, represent percentiles of a distribution. Thus, it is unclear why the authors don't present their results as z-scores. The use of percentiles makes this much more confusing and harder to compare to existing literature."

Our response: Thank you for this useful comment. We present the results as z-scores in the revised manuscript in order to increase comparability.
"Katherine Himes (Reviewer 2): This review is in response to the manuscript entitled, "The Association between Gestational Weight Gain Z-Score and Stillbirth: A Case-Control Study". This is a secondary data analysis of the Stillbirth Collaborative Research Network case-control study that examines the association between gestational weight gain and stillbirth at greater than 20 weeks. The authors found that low gestational weight gain is associated with an increased risk of stillbirth. They use gestational weight gain z-scores to operationalize gestational weight gain given the correlation between weight gain and gestational age at delivery. This is an important area of study and the authors have done a nice job making z scores accessible as they are not always intuitive. Limited comments are enumerated below.

1. Reviewer comment: "The etiology of stillbirth varies widely. I think the paper would be greatly strengthened by additional attempts to tease out the relationship between gestational weight gain and etiology of stillbirth."

Our response: Thank you for this valuable idea. The revised manuscript includes several sensitivity analyses that address this suggestion. We added sensitivity analyses separating early stillbirths (<28 weeks) from late stillbirths (≥28 weeks), as well as analyses separating preterm stillbirths (<37 weeks) from term stillbirths (≥37 weeks). We also analyzed intrapartum stillbirths separately from non-anomalous antepartum stillbirths.

Finally, we added some preliminary analyses for cause-of-death groupings and stillbirth. We chose 3 cause-of-death groupings which could biologically be associated with GWG and stillbirth and for which we had adequate sample size: 1) placental abnormalities (e.g., uteroplacental insufficiency, maternal vascular conditions, etc.), 2) maternal medical conditions other than hypertension (e.g., diabetes, antiphospholipid syndrome, thyroid disorder, etc.), and 3) obstetric complications during pregnancy (e.g., placental abruption; complications of multiple gestations; the combination of preterm labor, preterm premature rupture of membranes, and cervical insufficiency, etc.).

We view the 3 cause-of-death analyses as preliminary/hypothesis-generating for 2 reasons:

1. We were unable to analyze certain causes of death (e.g., hypertensive disorders) for which we lacked sample size.
2. Causes of fetal death were classified as probable causes, possible causes, or present conditions. We analyzed all stillbirths with probable causes, possible causes, or present conditions related to these three causes. Sample sizes of stillbirths with “probable” or “possible” causes of death were inadequate to allow us to analyze those separately.

2. Reviewer comment: "The authors use two different gestational weight gain z-score charts. This is a bit confusing to the reader as written. Is one chart better or worse for their data. The discrepancy between the two is confusing."

Our response: Thank you for your comment. We decided to remove the Intergrowth (FGLS) z-score standard from our paper because the Intergrowth charts were only available for normal weight women and for singleton pregnancies. Furthermore, the Hutcheon et al. z-score charts fit our data better than the Intergrowth charts. For instance, the mean and median z-scores in normal weight women with live births were −0.2 and −0.17, respectively, using Hutcheon et al.’s charts (SD= 0.96). In contrast, the mean and median z-scores in normal weight women were 0.37 and 0.42, respectively, using the Intergrowth charts (SD=1.14).

Minor points.

Reviewer comment: "Please outline all model confounders in the text for the ease of the reader."

Our response: All model confounders are now listed in the main text section.

Reviewer comment: "Please be clear about how maternal height and weight were ascertained-- I had difficulty finding it in the text."

Our response: Thank you for your comment. We added the following text to the methods section: “Data collection of consenting women included medical record abstraction, placental pathology, fetal autopsy, and postpartum maternal interview [21]. Most interviews were completed face-to-face before hospital delivery discharge; a few interviews were completed by telephone or other method within 4 weeks of delivery. Sociodemographic information was derived from the maternal interview. Maternal height, pre-pregnancy weight, weight at last prenatal visit, and weight at delivery were abstracted from medical records. If maternal height or pre-pregnancy weight were unavailable in the medical record, women’s self-reported height and pre-pregnancy weight data were taken from the maternal postpartum interview. Self-reported height and pre-pregnancy weight were used for only n=1 observation in our analysis.”