Author's response to reviews

Title: Prepregnancy Body Mass Index and Risk of Preterm Birth: Association Heterogeneity by Preterm Subgroups

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Dear Editorial Board:

Thank you for the opportunity to revise and resubmit our manuscript, “Prepregnacy BMI and Risk of Preterm Birth: Association Heterogeneity by Preterm Subgroups” (MS 6043112371124714). In this letter we respond point by point to the thoughtful critiques of the reviewers.

Reviewer #1 (Katherine Goetzinger)

1a) Patients were enrolled in the Boston Birth Cohort study starting in 1998. This particular study used data from 1998-2008; however, there are still only 4677 patients included. Clearly this is a much lower number than the expected volume over a ten-year period. Can the authors explain how these patients were selected?

To further clarify our recruitment strategy of preterm and low birth weight cases and controls, we added the statement: “Controls were matched by maternal age and race to cases in a 2:1 ratio.” (page 5, study population, paragraph 3)

1b) How many patients declined enrollment? This may introduce significant bias into the study.

Less than 10% of patients declined enrollment. We included a statement in our methods section. “More than 90% of mother-infant pairs approached for study participation enrolled in the study.” (page 5, study population, paragraph 3).

2) The preterm birth rate in the study is ~42% which is exceptionally high. While this is likely due the case-control study design of the original Boston Birth Cohort, this may effect your results given that preterm birth is the primary outcome studied.

We agree that the preterm birth rate in the study does not reflect the general U.S. population and is due to the original case-control study design of the original Boston Birth Cohort. We calculated odds ratios as appropriate for case-control study designs. We added a statement to our discussion section. “Our population may not be generalizable to others.”

3) Were cesarean deliveries included or excluded? It is unclear in the methods.

Cesarean deliveries were included in the analysis. To make this more clear, we added a statement in our methods: “Women have been recruited who delivered a singleton live infant, vaginally or by cesarean section, and meet the definition of a case…” (page 5, study population, paragraph 3).
4) Gestational weight gain was calculated as the difference between the last recorded weight before delivery and the self-reported prepregnancy weight. Was there a threshold of how long of an interval between last recorded weight and delivery could have lapsed?

We did not have a threshold for inclusion in the study based on the interval between last recorded weight and self-reported prepregnancy weight.

5a) Were records complete for each patient enrolled?

We included participants in this analysis with complete data for our main predictor, body mass index; and our main outcomes, preterm birth (gestational age at birth) and spontaneous vs medically induced birth (presentation prior to delivery abstracted from the medical record).

Missing data was denoted as “unknown” for chorioamnionitis, gestational weight gain, and household income in Table 1. We additionally had smaller amounts of missing data for hypertensive disorders of pregnancy (n =32), diabetes (n = 17), marital status (n = 14), alcohol or illicit drug use (n = 29), maternal stress (n = 30), cervical incompetence (n = 12) and placental previa (n = 10).

5b) How did the authors handle missing data?

For chorioamnionitis, gestational weight gain, household income, we coded missing data as a categorical variable in our models. For all other variables, the subject with the missing variable was not included in our models.

6) I would recommend changing the wording of your objective to “to evaluate the association between prepregnancy BMIa and early and late medically-induced and spontaneous PTB.

We have made this change (abstract).

Reviewer #2 (Asma Khalil)

1) The authors identified an association between pre-pregnancy obesity and medically induced PTB. They state that this association was “modestly attenuated” after adding hypertensive disorders of pregnancy and gestational diabetes to the model. In fact, these two conditions largely (almost completely) explain the association; this is what most practicing obstetricians expect, and is what their data show. Given this, they should consider altering the word ‘modestly’ to “largely” or similar (page 10, line 7). Similarly, they might re-word the relevant sentences in the Discussion section (page 11, line 9). Also in the conclusion section, the word “partially” should be replaced by largely (page 13, last line).

We have made the changes as indicated by the reviewer. Changes were made in the result section (page 10, paragraph 1), the discussion section (page 11, paragraph 2), and the conclusion section (page 13, paragraph 4).

2) Another of the authors’ notable conclusions is that pre-pregnancy obesity was associated with an apparent reduction in spontaneous PTB. I question whether this is truly and an independent association. Of all PTB, a third were induced for medical reasons. This will almost
certainly have removed from the study population a proportion of women who, had they not delivery expedited iatrogenically, might well have been destined for spontaneous PTB. This means that those with ongoing pregnancies would, as a group, be expected to have a lower rate of spontaneous PTB. In other words, the finding of an increased risk of medically induced PTB directly leads to the finding of a reduced rate of spontaneous PRB in the remaining women. I think that this is an important point, because as the paper is currently written, the reader might well be left with the conclusion that pre-pregnancy obesity directly protects against spontaneous PTB.

We agree with this comment and have added the following statement to our discussion section (page 12, paragraph 1). “Finally, it is possible that associations of maternal obesity and spontaneous PTB are inconsistent because of variable clinical thresholds for medical-induction. Obese women who are at risk for spontaneous PTB may instead deliver following medical-induction because of clinical concerns that differ by study population, thus changing the remaining pool of women at risk for spontaneous PTB.”

3) Discussion, page 13, Line 3: The authors recommend that “a continuum of gestational ages should be examined.” I would suggest that this analysis should be added to the manuscript.

We agree with this suggestion. We have performed this analysis. We added an additional statement to our methods section, “...we first used linear regression to examine the association of prepregnancy BMI and gestational weeks at delivery as a continuous variable.” (page 8, paragraph 3 to page 9, paragraph 1). We included the findings of this analysis in our results section: “...we found that, among all subjects, mothers with prepregnancy obesity delivered infants 0.28 weeks (95% C.I. [-0.54 to -0.03]) earlier than mothers with prepregnancy normal weight (data not shown). We found that this relationship was attenuated when hypertensive disorders of pregnancy (-0.28 to -0.07) and diabetes (-0.28 to -0.17), but not when chorioamnionitis (-0.28 to -0.30) was added to our model (data not shown). We...” (page 10, paragraph 1).

4) Title: BMI should be spelled out.

We have made this correction.

5) Abstract, Background: BMI should be spelled out the first time it is used, instead of in the following section.

We have made this correction.

6) Abstract, Results: the 95% CI for underweight contains 1 (not significant).

We agree that our CI of 0.99 to 2.16 (p-value 0.06) contains 1 as is therefore “not significant” per general accepted significance cut-point of p-values <0.05. We have changed our statement in the abstract to reflect this. “For spontaneous deliveries, prepregnancy obesity was associated with decreased odds of PTB (0.76 [0.58, 0.98]) and underweight was nearly associated with increased odds of PTB (1.46 [0.99, 2.16]).”

Yours sincerely,