Author’s response to reviews

Title: The Association between Maternal Blood Pressures and Offspring Size at Birth in Southeast Asian Women

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Author’s response to reviews: see over
Dear Editor,

Thank you for considering our manuscript “The Association between Maternal Blood Pressures and Offspring Size at Birth in Southeast Asian Women”. We appreciate the insightful critiques and comments from the reviewers.

As instructed, we have provided a point-by-point response to each of the comment raised by the reviewers, and have appended them at the end of this letter. Accordingly, we have also amended our manuscript with changes made during the revision (changes are highlighted in yellow). A clean copy of the revised manuscript has also been uploaded.

Should you have any additional requests or questions, please do not hesitate to contact me. We look forward to hearing from you.

Thank you.

Sincerely yours,

(On behalf of the authors)

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Reviewer #1 (Reviewer Comments):

This is an interesting and important study relating maternal blood pressure measurements in pregnancy to offspring size at birth. The majority of my comments are focused on the authors’ further justification, clarification and/or discussion about methods employed.

Major Compulsory Revisions:

1. It would be useful for the authors to address several issues related to maternal body size. First, the BMI that was adjusted for in the models (and used to evaluated interaction) seems to be a mid-pregnancy measure of BMI. Often, pre-pregnancy BMI is considered and it would be useful for the authors to discuss their reason for choosing the pregnancy measure.

   Thank you for your comment. Although pre-pregnancy BMI is often considered in other reports, we chose to use a mid-pregnancy BMI measured at 27 weeks gestation because of two reasons: (1) in our study, pre-pregnancy BMI was self-reported, and therefore more likely to be affected by information bias, e.g., overweight or obese women are likely to under-report their weight more than normal weight women; (2) 35 (4.9%) women did not report pre-pregnancy weight on the questionnaires.

   Conversely, the mid-pregnancy BMI measure was measured by investigators and therefore may be more reliable measure for maternal adiposity than pre-pregnancy BMI. However, we acknowledge that use of mid-pregnancy BMI may not fully reflect the obesity status of the participants due to the growing fetus and fluid accumulation from pregnancy. On the other hand, mid-pregnancy BMI was very strongly correlated with pre-pregnancy BMI (r=0.92). Therefore, we conducted a sensitivity analysis of adjusting pre-pregnancy BMI and rate of weight gain in the models, and we have included this in the revision as shown in Table S2.

   We have revised our Methods (Page 8, Line 17-19) and Discussion (Page 13, Line 13-17)

   Methods

   “(4) we adjusted for pre-pregnancy BMI and rate of weight gain instead of BMI at 27 weeks of gestation (n=678 due to 35 missing data for pre-pregnancy weight);” (Page 8, Line 17-19)

   Discussion

   “Third, the use of maternal BMI at 27 weeks gestation may be affected by misclassification due to the growing fetus and fluid accumulation. We chose to use mid-pregnancy BMI instead of pre-pregnancy BMI because the latter measure was self-reported and thus susceptible to information bias, and about 5% of the women did not report their pre-pregnancy weights.” (Page 13, Line 13-17)
2. Second, are the typical BMI cut-offs for overweight, obese the same during pregnancy? This information was not readily available. So, if a woman's BMI at 27 week is 28, is she considered overweight.

There is currently no standard BMI cut-offs for overweight and obesity during pregnancy, therefore, we used the WHO International BMI cut-offs for non-pregnant women as an indirect cut-off for maternal adiposity. Apart from the sensitivity analysis mentioned above, we have also re-evaluated the mid-pregnancy BMI categories using tertiles to test the interaction. Significant interactions have been observed, and the results have been added in the revision as Table S3 (Please see appended table)

We have added the following sentence in the Methods, Results and Discussion:

Methods
“(5) we used tertiles of BMI at 27 weeks gestation instead of the WHO classification as an alternative to test for interaction between maternal adiposity and blood pressures” (Page 8, Line 19-21)

Results
“Similar interactions were observed when tertiles of maternal BMI at 27 weeks gestation were used (Table S3)” (Page 9, Line 2-3)

Discussion
“Due to the lack of pregnancy-specific classification for obesity, we have used the WHO cut-offs for non-pregnant adults for overweight and obesity in our study. However, our sensitivity analysis of using tertiles of BMI suggested that the interaction with BMI categories was robust.” (Page 13, Line 17-19)

3. Finally, what about weight gain? Does a pre-pregnancy and time of delivery weight measure exist to evaluate the effect of weight gain? Weight gain is an important contributor to offspring birth size, but I'm less familiar with the association with blood pressure. This could be addressed in the discussion.

We were unable to measure maternal weight gain throughout pregnancy, as weight at the time of delivery was not captured in our study. Based on mid-pregnancy maternal weight, we have estimated the rate of maternal weight gain (calculated as weight difference between pre-pregnancy and mid-pregnancy weight in kg divided by length of gestation in weeks). We have adjusted for rate of weight gain in the models and the results were robust (Table S2).

“We did not measure maternal weight before delivery, and could not know whether the relation between blood pressure and size at birth outcomes would be changed if total weight gain during pregnancy was adjusted in the model.” (Page
4. I have some questions about Table 1. The manuscript says that table 1 evaluates maternal characteristics across blood pressures, but the table seems to look at blood pressures across maternal characteristics using ANOVA (methods). Is this what the authors intended? The table title is more accurate, but I'm still a little unclear what the intention was. Do the authors want to show how maternal characteristics change as blood pressure increases?

We apologize for the confusion. The main purpose for Table 1 was to show differences in maternal blood pressures by maternal characteristics. We have since made a correction to the text in Results.

“Women of Malay ethnicity, lower education levels and higher BMI categories were more likely to have higher peripheral and central blood pressures (p < 0.01, Table 1).” (Page 9, Line 7-9)

Minor Essential Revisions:

5. White, not Caucasian

We have replaced ‘Caucasian’ with ‘white’ in our manuscript.

6. There is no discussion about why one might expect to see racial differences in the association between BP and birth size. Is there biologic plausibility to explain?

Our main objective was to evaluate the relation between pregnancy blood pressures and offspring size at birth in Asian population. Because the GUSTO study included three Asian populations, we decided to conduct a secondary analysis to examine whether the relation could differ among ethnic groups. Our motivation to explore for ethnic modification also came about from a report by Lydakis et al. [1], where stronger relation between blood pressure and birth weight was reported in Asian Indians than white or black women.

To our awareness, our report on the inter-ethnic differences among Southeast Asian women is among the first few literature in Asian population. Therefore, we are unsure of the biological plausibility based on the limited literature available. Our analysis on the ethnic modification effect was a secondary sensitivity analysis, and we did not hypothesize that the association would be different in three ethnic groups.

Reference

In the revision, we have included the following sentences in the Discussion.

“However, we cannot exclude the possibility of ethnic differences due to the smaller subgroups of Indian and Malay women in our cohort and therefore was not powered to detect effect modification by maternal ethnicity. Our exploratory analysis on the ethnic differences in the relations between blood pressures and birth size were among the first few in literature and future studies are still needed to further explore the potential ethnic differences.” (Page 12, Line 15-20)

7. Was the study powered sufficiently in the first place to see any potential effect modification by ethnicity?

The interaction test usually requires a large sample size, particularly when the effect size is small. We acknowledge that the study was not powered sufficiently to see the potential effect modification by ethnicity, and included this as a limitation in the Discussion (as shown in the response to Question 6).

8. The authors address that smoking was self reported. Do the percentages of smokers seem reasonable considering the known (reported in the literature) prevalence of smoking for these populations?

Thank you for your advice. Based on Singapore’s National Health Survey in 2010 [1], the ethnic specific prevalence of smoking among women was 9.3% in Chinese women, 20.8% in Malay and 7.5% in Indian women aged between 18-39 years old. The smoking prevalence in our cohort is similar at 9.7% in Chinese, 25.5% in Malay and 5.1% in Indian women. As our smoking prevalence are similar to our national prevalence rates, we have removed this from our limitations.

Reference

9. Mention of additional unmeasured confounders (diet, exercise, for example).

We acknowledge that unmeasured confounding is possible in our study, like maternal diet and physical activity. Various studies have confirmed that maternal diet in pregnancy [1-4] and physical activity [3, 5] have been found to be associated with hypertension and/or blood pressures. Meanwhile, evidence from epidemiological studies have shown that maternal diet [6-8], and physical activity [9] can affect offspring birth weight. Therefore, maternal diet and physical activity may potentially confound our results as they have been shown to be associated with both maternal hypertension and birth weight.

Reference


We have further elaborated this in Discussion.

“Our results may also be affected by residual confounding from coffee intake as it was self-reported, and unmeasured confounding factors, like diet and physical activity, are possible to explain our results.” (Page 13, Line 22-24)

10. Were the size of birth measurements taken by study staff or were these extracted from medical records?

We have clarified in the Methods section that the size of birth measures were extracted from medical records.

“Information on offspring size at birth (weight, length, head circumference and placental weight) were extracted from medical records, which were measured by midwives according to standard hospital protocols.” (Page 7, Line 14-16)
Discretionary Revisions

11. In results, add n's by ethnicity (not just %)

We have added the number of participants by ethnicity in Results section.

“Oh of the 713 women studied, 339 (55.9%) were Chinese, 196 (27.5%) were Indians and 118 (16.6%) were Malays.” (Page 9, Line 3-4)

Reviewer #2 (Reviewer Comments):

1. Is the question posed by the author well defined? The question is well defined. However, I wonder whether the authors can strengthen the justification and innovation of the study.

1.1 In the background we see that most studies are consistent and in the conclusion we see that the prospective studies were all consistent and the inconsistencies were seen in the retrospective studies. Why do we therefore need another prospective study looking at the same question?

Thank you for your comment and suggestion. Although prospective studies, in general, have observed a consistent inverse linear association between maternal blood pressures and size at birth outcomes, studies with simultaneous assessment of both maternal peripheral and central blood pressures are still lacking and previous studies were limited in sample size. In addition, despite the higher incidence of small for gestational age in Southeast Asian women [1], the relation between pregnancy blood pressures and size at birth are poorly reported in these women [2-4]. Finally, none of the studies have included the three major Asian ethnic groups in one study and explore the potential ethnic differences.

Reference
Therefore, the current study was aimed to build on previous work by addressing these specific gaps. We have emphasized these gaps and have included our study rationale in Background.

“There is evidence that the relation between maternal blood pressures and offspring’s birth weight were found to be stronger in Asian Indians than white or black women [15], and was more evident in normal weight women than obese women [6]. As the incidence of small for gestational age in Southeast Asian women is one of the highest in the world [18], examining inter-ethnic variation may enable specific and appropriate public health interventions.” (Page 5, Line 16-20)

1.2 In addition the effect modification by obesity has already been studied. One thing stressed was the simultaneous evaluation of various blood pressures as well as modification effects. The authors should explain why is simultaneous evaluation important?

In order to examine the relations between maternal blood pressures and offspring size at birth, we have simultaneously measured maternal central and peripheral blood pressures so as to enable comparisons across these blood pressure measures. The role of central blood pressures in offspring size at birth may be of interest as there is evidence to suggest that the relation between maternal central blood pressures and size at birth may be more pronounced than peripheral blood pressures [1, 2]. However, very few studies have examined both peripheral and central blood pressures and the sample sizes in previous studies are small [1-3].

Reference

We have made appropriate changes in Background (Page 5, Line 9-15) and Discussion (Page 11, Line 16-23).

Background
“Several studies have investigated the associations between offspring’s birth weight and maternal peripheral [3, 5-17] and central blood pressures [9, 13, 14], with inverse relations reported in most studies [3, 5-9, 13-17], but not all [10-12].
Some studies have also suggested that the relation between maternal central blood pressures and size at birth may be more pronounced than peripheral blood pressures [13, 14]. However, very few studies have examined both peripheral and central blood pressures and the sample sizes were small in previous studies [9, 13, 14].” (Page 5, Line 9-15)

**Discussion**

“Some studies have suggested that central blood pressures may be more relevant to size at birth than the conventional peripheral blood pressures, because blood pressure differences were more pronounced in central than peripheral measures [13, 14]. However, in the current analysis, we found similar effect estimates between central and peripheral blood pressures, which is consistent with an earlier report by Elvan-Taspinar et al. [9]. Although central blood pressures may be better markers for arterial stiffness [23, 25], the role of central and peripheral blood pressures in relation to offspring birth size have yet to be ascertained due to the limited and divergent literature” (Page 11, Line 16-23)

1.3 The other innovation is the modification by maternal ethnicity in this particular population. Maybe addressing why ethnic differences within the Asian population is important can help add to the justification of the study.

There were few studies examining the relation between maternal blood pressure and offspring size in Asian women. By examining this in a cohort of Southeast Asian women, and to explore their ethnic differences, we hope to better inform public health prevention as Southeast Asia has the highest incidence of small for gestational age.

We have included this in our study rationale in Background (Page 5, Line 17 - 23). Please see point 1.1.

1.4 Also, blood pressure in this study is conducted in the second trimester. When is blood pressure measured in the other studies mentioned? Maybe the findings specific to the trimester timing in this study is something interesting to mention.

At present, we are unsure of any gestation specific blood pressure findings due to the inconsistent reports from studies that have examined repeated blood pressure measures [1, 2] or at a single time point [3-8]. In a cohort of 8623 women with repeated peripheral blood pressure measures from 1st – 3rd trimesters and followed till delivery, inverse relations between blood pressures and birth size were found only at 3rd trimester [1]. But in another cohort of 50 women with peripheral and central blood pressures measured at 2nd and 3rd trimesters, null associations were reported across the two trimesters for peripheral blood pressures but inverse associations for central blood pressures [2].
Other studies with single measure of blood pressures were not conclusive as well because most of these studies [3-6] had blood pressures measured at 3rd trimester, except for one perinatal cohort study which measured 2nd trimester peripheral blood pressure [8]. In addition, findings from studies with a single measure of 3rd trimester blood pressure were inconsistent, with some reporting linear [3-6] associations but in another, a u-shaped [7] associations. As for 2nd trimester peripheral blood pressure, a null association was reported in relation to low birth weight [8].

Reference

2. Are the methods appropriate and well described?
The methods are very well described and fit the study question well. Yet the authors should clarify several issues.
2.1 The maternal BMI variable is categorized based on BMI recommendations for "normal" women. The authors should try and incorporate what is recommended/expected for pregnant women? Since this is a central part of the effect modification analyses, I am wondering whether things would look different if a pregnancy-specific variable was used.

As discussed for the Reviewer 1, we chose to use a mid-pregnancy BMI
measured at 27 weeks gestation because of two reasons: (1) in our study, pre-pregnancy BMI was self-reported, and therefore more likely to be affected by information bias, e.g., overweight or obese women are likely to under-report their weight more than normal weight women; (2) 35 (4.9%) women did not report pre-pregnancy weight on the questionnaires.

We have conducted a sensitivity analysis of adjusting pre-pregnancy BMI and rate of weight gain, and the results were essentially the same (Table S2). Furthermore, we have used tertiles of mid-pregnancy BMI to test the interaction, and again, significant interactions were observed between tertiles of BMI and blood pressures for the offspring birth size measures (Table S3).

2.2 I am not sure if the authors have a maternal weight taken at baseline, but if they do, it may make sense to consider gestational weight gain or something similar to IOM recommendation (though that is for overall pregnancy weight gain).

As discussed above, the pre-pregnancy weight was self-reported and there were some missing data as well. The results did not change if we controlled for pre-pregnancy BMI and rate of weight gain (Table S2). However, maternal weight at delivery was not measured and we could not capture the overall pregnancy weight gain.

2.3 Since gestational age would clearly affect offspring size, why was this not adjusted for in the main analyses and only looked at in the sensitivity analyses?

We apologize for the lack of clarity. We have adjusted for gestational age in the analysis. This was done by including a continuous variable of gestation weeks at delivery in our models. In our sensitivity analysis, we have converted birth weight, length and head circumference into gestation specific standard deviation scores prior to including them into the analysis models. This was done to better account for the effect of gestational duration on size at birth. As shown in Tables S4-S6, the conclusions remained unchanged.

In our revision, we have clarified the description of the adjusted variables in Methods (Page 8, Line 1-3).

“All analyses were adjustment for baby's gender, gestation age at delivery in weeks, maternal age, ethnicity, education, parity, smoking history, height, BMI at 27 weeks gestation, coffee consumption and depression.” (Page 8, Line 1-3)

2.4 The authors mention results based on offspring size continuously and as a binary variable. Although it seems obvious, but this should be spelled out in the methods a bit more clearly (e.g "Information on offspring size at birth were measured...Both exact and categorical birth weights were recorded." or "The relationship between blood pressures and size at birth were examined using multiple linear and logistic regression models for continuous and binary BIRTH
SIZE outcomes, respectively."

We apologized for the lack of clarity. We have revised the wording in Methods (Page 7, Line 18-20).

“The binary outcome of low birth weight was defined as weight at birth <2500 g and small for gestational age was defined as those who were below the 10th percentile for gestational age adjusted birth weight.” (Page 7, Line 18-20)

2.5 Were peripheral systolic and diastolic blood pressures taken after few minutes of rest? If yes, please state.

Thank you for your comment. The study participants were rested for at least 10 minutes prior to the first blood pressure measurement. We have included this description in Methodology (Page 7, Line 4-5).

“Study participants were rested for at least 10 minutes prior to the first blood pressure measurement.” (Page 7, Line 4-5)

2.6 Authors should include a description of the statistical modelling used to test the interactions.

We apologized for the lack, and we have included a description in Methodology (Page 8, Line 5-10).

“We further evaluated the potential effect modification by maternal ethnicity (Chinese, Indian, or Malay) and BMI categories (normal, overweight, or obese). Multiplicative interaction terms with blood pressures as continuous variable and ethnicity or BMI as categorical variable were added to the final model, and the likelihood ratio test was used to test for significance. We also reported the results stratified by maternal ethnicity (Chinese, Indian, or Malay) and BMI category (normal weight, overweight, or obese).” (Page 8, Line 5-10)

3. Are the data sound?

3.1 Ethnic distribution in text does not match that in the Table.

We apologize for the error, and a correction has been made to the text in Results (Page 9, Line 3-4).

“Of the 713 women studied, 339 (55.9%) were Chinese, 196 (27.5%) were Indians and 118 (16.6%) were Malays.” (Page 9, Line 3-4)

3.2 Some of the results presented in the first paragraph of the results section are shown in Suppl. Table 1 and not just in Table 1.
We apologize for the lack of clarity. We have referenced Supplementary Table 1 accordingly in Results (Page 9, Line 5).

3.3 The authors state in the 2nd paragraph of the results section that the association between peripheral SBP and BW was observed only after adjustment for maternal and fetal covariates. Do they present at all results from unadjusted models?

We apologize for the lack of clarity in our text. We have amended our text, to keep to the adjusted results as shown in Results (Page 9, Line 10-12).

“After adjusting for maternal and fetal covariates, central SBP was inversely associated with all birth measures, and peripheral SBP was inversely associated with birth weight (all p < 0.05; Table 2).” (Page 9, Line 10-12)

3.4 On page 9, 2nd paragraph the authors describe null finding with regards to BP*ethnicity interactions on size at birth. It will help the reader to know the power for detecting such an interaction with the given sample size.

The primary objective of our study was to examine the relations between maternal blood pressures and offspring size at birth. Since we had the data from the three ethnic groups, we conducted the secondary analysis to evaluate the potential interaction between maternal blood pressures and ethnicity. The analysis were exploratory in nature, and therefore our sample size was underpowered to test the interactions. Nonetheless, we performed the stratified analysis because of the lack in literature examining ethnic differences in relation to maternal hypertension and birth weight, and the high incidences of small for gestational age in Southeast Asian women. It is hoped that our findings may stimulate and provide the basis for further research.

In our revision, we have clarified that the evaluation for BP*ethnic modification was an exploratory analysis, and have included the lack of power as a study limitation in our discussion (Page 12, Line 15-20).

“However, we cannot exclude the possibility of ethnic differences due to the smaller subgroups of Indian and Malay women in our cohort and therefore was not powered to detect effect modification by maternal ethnicity. Our exploratory analysis on the ethnic differences in the relations between blood pressures and birth size were among the first few in literature and future studies are still needed to further explore the potential ethnic differences.” (Page 12, Line 15-20)

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? YES

Thank you for your positive comment!
5. Are the discussion and conclusion well balanced and adequately supported by the data? Yes. It is very nicely balanced. Each topic briefly touched on in the introduction is nicely followed-up and elaborated in the discussion based on previous literature as well as the study's results.

Thank you for your positive comment!

5.1 One point to clarify, when the authors describe the consistency among studies with regard to the inverse association between maternal blood pressures and offspring size at birth, they should specify the stage of pregnancy when the blood pressure was measured. Is it in the second trimester, similar to the current study? Bakker actually measured BP at all three trimesters?

Thank you for your comment and suggestion. Compared with Bakker et al who examined maternal blood pressures at the 3 pregnancy trimesters (at mean gestations 13.2, 20.4 and 30.2 weeks), our blood pressure measurement at late 2nd trimester [median gestation of 27 weeks (interquartile range 26 to 29 weeks)] was close to their blood pressure measure taken at 3rd trimester [mean 30.2 weeks (range 28.4–32.9 weeks)] measurement. Due to the overlapping periods of measurement, we consider that our results are consistent with Bakker et al.

We have also included descriptions detailing the timing of blood pressure measurement for other studies in Discussion (Page 10, Line 21 to Page 11, Line 7).

“For example, Bakker et al. [5] reported that per one-SD increase in SBP and DBP at mean gestation 30.2 weeks (range 28.4 to 32.9 weeks) was associated with 16.9 g and 50.6 g lower birth weight, respectively. Among non-hypertensive women, higher peripheral blood pressures (range of gestation: 26 to 39 weeks) were also associated with lower birth weight [9]; and higher central blood pressures (range of gestation 22 to 39 weeks) were associated with lower birth weight [13, 14]. However, there are studies with conflicting results. For example, two previous studies measuring DBP from 34 weeks gestation onwards [12] and the average of SBP and DBP during pregnancy [10] have described a u-shaped association with birth weight. In another perinatal cohort study, DBP measured between 15 to 24 weeks gestation were not found to be significantly associated with birth weight [11].” (Page 10, Line 21 to Page 11, Line 7)

6. Are the limitations of the work clearly stated? Yes. Though again,

6.1 I would like to know whether gestational weight gain or the ability to look at weight/BMI in relation to pregnancy could be assessed, as these are strongly related to birth weight.

We have assessed maternal BMI and weight gain based on available data at 27 weeks gestation (Please see appended Tables S2-S3) to assess the robustness of our
results. We have included the lack of assessment of pregnancy weight gain as our study limitation.
### Table S2. Sensitivity Analysis for per 1-SD Increase in Maternal Blood Pressures and Size at Birth

<table>
<thead>
<tr>
<th></th>
<th>Peripheral Systolic Blood Pressure (1 SD = 11.1 mmHg)</th>
<th>Peripheral Diastolic Blood Pressure (1 SD = 8.3 mmHg)</th>
<th>Central Systolic Blood Pressure (1 SD = 10.0 mmHg)</th>
<th>Central Pulse Pressure (1 SD = 6.5 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weight (g)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Main Model</td>
<td>713</td>
<td>-35.56 (-66.57 to -4.54)</td>
<td>-25.13 (-55.36 to 5.09)</td>
<td>-40.52 (-70.66 to -10.37)</td>
</tr>
<tr>
<td>Main Model + GDM*</td>
<td>663</td>
<td>-34.47 (-66.93 to -1.99)</td>
<td>-32.77 (-64.51 to -1.03)</td>
<td>-41.72 (-73.05 to -10.38)</td>
</tr>
<tr>
<td>Main Model among non-hypertensive women</td>
<td>705</td>
<td>-36.25 (-68.02 to -4.47)</td>
<td>-30.16 (-61.28 to 0.97)</td>
<td>-42.63 (-73.65 to -11.61)</td>
</tr>
<tr>
<td>Main Model using multiple imputation</td>
<td>922</td>
<td>-34.00 (-65.25 to -2.75)</td>
<td>-24.37 (-53.15 to 4.41)</td>
<td>-38.43 (-67.47 to -9.39)</td>
</tr>
<tr>
<td>Main Model with pre-pregnancy BMI &amp; rate of weight gain</td>
<td>678</td>
<td>-35.05 (-66.66 to -3.43)</td>
<td>-21.19 (-51.69 to 9.33)</td>
<td>-40.14 (-70.79 to -9.49)</td>
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<tr>
<td>Length (cm)**</td>
<td></td>
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<tr>
<td>Main Model</td>
<td>711</td>
<td>-0.16 (-0.32 to 0.01)</td>
<td>-0.10 (-0.27 to 0.06)</td>
<td>-0.19 (-0.36 to -0.03)</td>
</tr>
<tr>
<td>Main Model + GDM*</td>
<td>661</td>
<td>-0.17 (-0.35 to 0.00)</td>
<td>-0.14 (-0.31 to 0.04)</td>
<td>-0.21 (-0.38 to -0.04)</td>
</tr>
<tr>
<td>Main Model among non-hypertensive women</td>
<td>703</td>
<td>-0.18 (-0.36 to -0.01)</td>
<td>-0.14 (-0.31 to 0.02)</td>
<td>-0.23 (-0.40 to -0.06)</td>
</tr>
<tr>
<td>Main Model using multiple imputation</td>
<td>921</td>
<td>-0.16 (-0.32 to 0.01)</td>
<td>-0.11 (-0.27 to 0.05)</td>
<td>-0.21 (-0.37 to -0.06)</td>
</tr>
<tr>
<td>Main Model with pre-pregnancy BMI &amp; rate of weight gain</td>
<td>676</td>
<td>-0.15 (-0.32 to 0.02)</td>
<td>-0.10 (-0.27 to 0.06)</td>
<td>-0.19 (-0.36 to -0.02)</td>
</tr>
</tbody>
</table>
**Head circumference (cm)**

<table>
<thead>
<tr>
<th>Model Type</th>
<th>N</th>
<th>Weight Estimate</th>
<th>95% CI</th>
<th>Weight Estimate</th>
<th>95% CI</th>
<th>Weight Estimate</th>
<th>95% CI</th>
<th>Weight Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
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<td>-0.09 (-0.19 to 0.02)</td>
<td>-0.08 (-0.18 to 0.02)</td>
<td>-0.12 (-0.23 to -0.02)</td>
<td>-0.07 (-0.16 to 0.02)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Main Model + GDM*</td>
<td>661</td>
<td>-0.07 (-0.19 to 0.04)</td>
<td>-0.07 (-0.18 to 0.04)</td>
<td>-0.10 (-0.21 to 0.01)</td>
<td>-0.05 (-0.15 to 0.05)</td>
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<tr>
<td>Main Model among non-hypertensive women</td>
<td>703</td>
<td>-0.10 (-0.21 to 0.01)</td>
<td>-0.10 (-0.21 to 0.01)</td>
<td>-0.14 (-0.25 to -0.04)</td>
<td>-0.07 (-0.17 to 0.02)</td>
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<tr>
<td>Main Model using multiple imputation</td>
<td>921</td>
<td>-0.08 (-0.20 to 0.03)</td>
<td>-0.08 (-0.18 to 0.03)</td>
<td>-0.12 (-0.22 to -0.01)</td>
<td>-0.06 (-0.15 to 0.04)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Main Model with pre-pregnancy BMI &amp; rate of weight gain</td>
<td>676</td>
<td>-0.09 (-0.20 to 0.02)</td>
<td>-0.08 (-0.18 to 0.03)</td>
<td>-0.12 (-0.23 to -0.02)</td>
<td>-0.07 (-0.17 to 0.02)</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Placenta weight (g)**

<table>
<thead>
<tr>
<th>Model Type</th>
<th>N</th>
<th>Weight Estimate</th>
<th>95% CI</th>
<th>Weight Estimate</th>
<th>95% CI</th>
<th>Weight Estimate</th>
<th>95% CI</th>
<th>Weight Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main Model</td>
<td>699</td>
<td>-8.78 (-18.74 to 1.19)</td>
<td>-6.94 (-16.63 to 2.76)</td>
<td>-11.16 (-20.85 to -1.47)</td>
<td>-6.44 (-15.04 to 2.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main Model + GDM*</td>
<td>650</td>
<td>-11.48 (-22.05 to -0.92)</td>
<td>-9.19 (-19.51 to 1.13)</td>
<td>-13.27 (-23.46 to -3.07)</td>
<td>-7.12 (-16.32 to 2.08)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main Model among non-hypertensive women</td>
<td>691</td>
<td>-8.93 (-19.17 to 1.31)</td>
<td>-7.70 (-17.72 to 2.32)</td>
<td>-11.54 (-21.54 to -1.54)</td>
<td>-5.92 (-14.65 to 2.80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main Model using multiple imputation</td>
<td>908</td>
<td>-8.04 (-18.21 to 2.13)</td>
<td>-8.23 (-17.39 to 0.93)</td>
<td>-11.23 (-21.31 to 1.14)</td>
<td>-5.64 (-13.92 to 2.65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main Model with pre-pregnancy BMI &amp; rate of weight gain</td>
<td>666</td>
<td>-11.15 (-21.45 to -0.85)</td>
<td>-7.79 (17.70 to 2.12)</td>
<td>-13.01 (-22.99 to -3.02)</td>
<td>-7.59 (-16.43 to 1.24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval; GDM, gestational diabetes; IOM, Institute of Medicine

* There were 50 women with missing information on gestational diabetes

** There were 2 women with missing information on length and head circumference.

*** There were 14 women with missing information on placental weight.

Main model was derived from multiple linear regression with adjustment for baby's gender, gestation at delivery, maternal age, ethnicity, education, parity, smoking history, maternal BMI at 27 weeks gestation, height, coffee consumption and depression.
Main Model + GDM: adjusted for covariates in Main Model with additional adjustment for gestational diabetes.

Main Model among non-hypertensive women: the analysis was done in women with peripheral systolic blood pressures less than 140 mmHg and diastolic blood pressures less than 90 mmHg.

Main Model using multiple imputation: missing data in blood pressures were imputed from model with maternal age, ethnicity, education, parity, smoking history, BMI at 27 weeks gestation, height, gestational diabetes and the respective outcome variable.

Main Model with pre-pregnancy BMI is adjusted for the same covariates in Main Model except for maternal BMI at 27 weeks gestation which was replaced by pre-pregnancy BMI and rate of weight gain per week.
Table S3. Per 1-SD Increase in Maternal Blood Pressures and Size at Birth by Maternal BMI in Tertiles*

<table>
<thead>
<tr>
<th>Maternal BMI in Tertiles</th>
<th>β (95% CI) Peripheral Systolic Blood Pressure (1 SD = 11.1 mmHg)</th>
<th>β (95% CI) Peripheral Diastolic Blood Pressure (1 SD = 8.3 mmHg)</th>
<th>β (95% CI) Central Systolic Blood Pressure (1 SD = 10.0 mmHg)</th>
<th>Central Pulse Pressure (1 SD = 6.5 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Tertile</td>
<td>-89.57 (-142.41 to -36.73)</td>
<td>-32.09 (-82.41 to 18.23)</td>
<td>-95.6 (-145.66 to -45.54)</td>
<td>-84.53 (-129.73 to -39.33)</td>
</tr>
<tr>
<td>2nd Tertile</td>
<td>-25.05 (-77.64 to 27.53)</td>
<td>-53.05 (-103.05 to -3.05)</td>
<td>-26.05 (-76.72 to 24.62)</td>
<td>24.38 (-21.83 to 70.59)</td>
</tr>
<tr>
<td>3rd Tertile</td>
<td>2.21 (-57.05 to 61.47)</td>
<td>14.56 (-44.92 to 74.04)</td>
<td>-6.28 (-65.48 to 52.92)</td>
<td>-21.13 (-72.20 to 29.93)</td>
</tr>
<tr>
<td><strong>Length (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Tertile</td>
<td>-0.54 (-0.85 to -0.22)</td>
<td>-0.14 (-0.45 to 0.16)</td>
<td>-0.58 (-0.88 to -0.28)</td>
<td>-0.57 (-0.84 to -0.30)</td>
</tr>
<tr>
<td>2nd Tertile</td>
<td>0.08 (-0.21 to 0.37)</td>
<td>-0.27 (-0.54 to 0.00)</td>
<td>-0.01 (-0.29 to 0.26)</td>
<td>0.28 (0.03 to 0.53)</td>
</tr>
<tr>
<td>3rd Tertile</td>
<td>-0.03 (-0.33 to 0.27)</td>
<td>0.18 (-0.12 to 0.48)</td>
<td>0.00 (-0.30 to 0.30)</td>
<td>-0.17 (-0.43 to 0.09)</td>
</tr>
<tr>
<td><strong>Head circumference (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Tertile</td>
<td>-0.31 (-0.49 to -0.12)</td>
<td>-0.22 (-0.40 to -0.05)</td>
<td>-0.30 (-0.48 to -0.12)</td>
<td>-0.13 (-0.29 to 0.03)</td>
</tr>
<tr>
<td>2nd Tertile</td>
<td>-0.06 (-0.24 to 0.13)</td>
<td>-0.12 (-0.30 to 0.06)</td>
<td>-0.10 (-0.28 to 0.08)</td>
<td>0.01 (-0.16 to 0.17)</td>
</tr>
<tr>
<td>3rd Tertile</td>
<td>0.08 (-0.12 to 0.28)</td>
<td>0.11 (-0.09 to 0.31)</td>
<td>0.01 (-0.19 to 0.21)</td>
<td>-0.10 (-0.27 to 0.08)</td>
</tr>
</tbody>
</table>

*P for interaction

| Weight (g) | 0.03 | 0.09 | 0.03 | 0.008 |
| Length     | 0.02 | 0.06 | 0.006| 0.0001|
| Head circumference (cm) |0.005|0.009|0.02|0.64|
**Placenta weight**

<table>
<thead>
<tr>
<th>Tertile</th>
<th>N</th>
<th>1st Tertile (g)</th>
<th>2nd Tertile (g)</th>
<th>3rd Tertile (g)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>230</td>
<td>-28.89 (-47.19 to -10.59)</td>
<td>-16.57 (-33.81 to 0.66)</td>
<td>-29.41 (-46.89 to -11.93)</td>
<td>-17.04 (-32.46 to -1.63)</td>
</tr>
<tr>
<td>2nd</td>
<td>240</td>
<td>6.60 (-9.09 to 22.29)</td>
<td>-6.38 (-21.45 to 8.68)</td>
<td>0.12 (-15.04 to 15.28)</td>
<td>7.06 (-6.71 to 20.82)</td>
</tr>
<tr>
<td>3rd</td>
<td>229</td>
<td>-8.07 (-26.95 to 10.81)</td>
<td>-1.07 (-19.94 to 17.81)</td>
<td>-9.83 (-28.60 to 8.95)</td>
<td>-10.18 (-26.30 to 5.94)</td>
</tr>
</tbody>
</table>

SD, standard deviation; CI, confidence interval; BMI, body mass index.

* Multiple linear regression models were used with adjustment for baby's gender, gestation at delivery, maternal age, ethnicity, education, parity, smoking history, height, BMI at 27 weeks gestation, coffee consumption and depression.

** There were 2 women with missing information on length and head circumference.

*** There were 14 women with missing information on placental weight.