

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Does pre-pregnancy BMI determine blood pressure during pregnancy? A prospective cohort study
<b>AUTHORS</b>	Savitri, Ary; Zuithoff, Nicolaas; Browne, Joyce; Amelia, Dwirani; Baharuddin, Mohammad; Grobbee, Diederick; Uiterwaal, Cuno

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Cassandra Spracklen University of North Carolina at Chapel Hill
<b>REVIEW RETURNED</b>	07-Apr-2016

<b>GENERAL COMMENTS</b>	<p>The manuscript focusing on prepregnancy BMI, gestational weight gain, and gestational blood pressure and their associations with GH and PE is well written and easy to understand. The findings are well described.</p> <p>This reviewer understands the reasoning behind the use of BMI tertiles for analysis; however, a statement of the range of BMIs in each tertile would be very useful and informative.</p> <p>An unstated limitation of this study is the amount of study participants with limited blood pressure measurements. For a longitudinal analysis, it seems troubling that 20% of the included subjects only had one blood pressure reading and another 17% only had two readings, particularly when the outcomes of interest are preeclampsia and gestational hypertension. When were these 1-2 measurements taken? How do you know a subject doesn't have GH or PE if they never had their blood pressures checked? The authors should mention this limitation and address its impact on the study. A sensitivity analysis including only those subjects known, for sure, to not have GH or PE would also be useful.</p>
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<b>REVIEWER</b>	Dayeon Shin Department of Food Science and Human Nutrition, Michigan State University, East Lansing, MI, USA
<b>REVIEW RETURNED</b>	18-Apr-2016

<b>GENERAL COMMENTS</b>	<p>The paper aimed to evaluate if prepregnancy BMI and pregnancy weight gain are associated with gestational hypertension and preeclampsia in Indonesian pregnant women. Although of potential interest to the readers of the journal, I have a number of concerns that I believe should be addressed.</p> <p>Abstract</p>
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	<p>-Page 2, lines 8 &amp; 39: Please be consistent using the terminology, "pregnancy weight gain" vs. "gestational weight gain" throughout the manuscript.</p> <p>Strengths and limitations of this study</p> <p>-Page 3, Line 10: "Women were classified into the tertiles of their prepregnancy BMI" -&gt; why is this one of the strengths of the study? Please find other strength of this research.</p> <p>Introduction</p> <p>-Page 4: Please add statements regarding why gestational hypertension and preeclampsia problem including long-term health consequences.</p> <p>Methods:</p> <p>-Page 4, line 53-54: Explain what "socioeconomic background" is.</p> <p>-Page 5, line 7: what are "previous complications and family history disease"? Please define them.</p> <p>-Page 5, line 41: what is the difference between "confounding variables" vs. "intermediate variables"? The authors simply controlled for gestational weight gain in the "explanatory model". How is this different from the confounding variable?</p> <p>-Page 6, line 6: were there any post-term births (&gt;42 weeks)?</p> <p>-Page 6, line 15: why did the authors divided prepregnancy BMI into tertiles? If previous literature recommended a lower cut-off for overweight/obesity in Asian population, how about dividing prepregnancy BMI into four categories based on "Asian criteria BMI cut-off points (Underweight: &lt;18.5, normal weight: 18.5-22.9, overweight: 23.0-24.9, obese: &gt;=25.0 kg/m<sup>2</sup>)?"</p> <p>Results &amp; Discussion:</p> <p>-Page 7, lines 29-32 &amp; Page 10, line 36: "Prepregnancy weight gain did not mediate the effect of prepregnancy BMI on blood pressure level during pregnancy". How did the authors come with mediation effect? Please elaborate more results on Table 2 where the authors perform mixed linear regression such as coefficient between 1) prepregnancy BMI and blood pressure; 2) prepregnancy BMI and pregnancy weight gain; 3) prepregnancy weight gain and blood pressure. Without these results, it is not appropriate for the authors to conclude the mediation effect of prepregnancy weight gain between prepregnancy BMI and blood pressure level.</p> <p>-Page 9, line 17: prepregnancy BMI is not a perfect measure of adiposity (women with higher muscles may have higher BMI compared to women with lower muscles with same weight). It is possible women with similar prepregnancy BMI have varying distribution of adipose tissue (Romero-Corral et al., 2008).</p> <p>-Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. <i>Int J Obes (Lond)</i> 2008;32(6):959–966.</p>
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	<p>-Page 10, line 12: spell out "HELLP syndrome".</p> <p>-Page 10, lines 44-47: The authors stated that excessive gestational weight gain is a determinant of gestational hypertension. Did the authors consider categorizing gestational weight gain into three groups based on the Institute of Medicine's recommendation: inadequate, adequate and excessive gestational weight gain and found the association between the excessive gestational weight gain and gestational hypertension and preeclampsia?</p> <p>-Page 11, line 53: see the previous comment regarding the "mediation effect" and revise the sentence "prepregnancy weight gain does not appear to mediate these effects".</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Cassandra Spracklen

Institution and Country: University of North Carolina at Chapel Hill

Please state any competing interests or state 'None declared': None declared

Comment:

The manuscript focusing on prepregnancy BMI, gestational weight gain, and gestational blood pressure and their associations with GH and PE is well written and easy to understand. The findings are well described.

This reviewer understands the reasoning behind the use of BMI tertiles for analysis; however, a statement of the range of BMIs in each tertile would be very useful and informative.

Response:

We thank the reviewer for the compliment. In table 1, besides describing the median of BMI, we have now added the minimum and maximum value of BMI in each tertile.

Comment:

An unstated limitation of this study is the amount of study participants with limited blood pressure measurements. For a longitudinal analysis, it seems troubling that 20% of the included subjects only had one blood pressure reading and another 17% only had two readings, particularly when the outcomes of interest are preeclampsia and gestational hypertension. When were these 1-2 measurements taken? How do you know a subject doesn't have GH or PE if they never had their blood pressures checked? The authors should mention this limitation and address its impact on the study. A sensitivity analysis including only those subjects known, for sure, to not have GH or PE would also be useful.

Response:

It is true that 409 women (20%) in this study had only one measurement of blood pressure (BP). Half of the women were referred to the hospital at a later stage of pregnancy due to complications, including gestational hypertension, of whom 10 of these women were diagnosed with. The other only came once for antenatal care visit in the hospital where this study was conducted, and later paid visit and gave birth at other health care facilities. It is indeed difficult to rule out the possibility of GH and PE in these women and we agree that this is a limitation of the present study. A statement about this has been added in the discussion section, third paragraph.

At the reviewer's suggestion, sensitivity analyses on the associations between prepregnancy BMI and blood pressure during pregnancy have now been performed by restricting the analysis to women with 2 or more, 3 or more, and 4 or more BP measurements. The results are presented in the

supplementary file in Supplement 2, 3, and 4. As compared to the results shown in Table 2, results from the sensitivity analyses were not different from the overall analysis. Furthermore, sensitivity analysis on the associations between pre-pregnancy BMI and risk of GH and PE has also been performed. Analyses within women with 2 or more, 3 or more, and 4 or more BP measurements as shown in Supplement 5, 6, and 7, respectively. Again, these analyses gave results that are comparable to the results in Table 3. Therefore, we conclude that the results shown in Table 2 and 3, which also include women with one BP measurements are relatively unbiased.

A sensitivity analysis including only women who were known for sure to not have GH or PE, as suggested by the reviewer, implies that analyses should only be performed in women with 2 or more BP measurements who were not diagnosed with GH and PE. In the overall approach we prefer to not exclude women with GH and PE from the analysis, since it did not represent our study domain which is pregnant women irrespective their GH or PE status. However, we also performed the suggested analysis and present the results in Supplement 8. The results are, again, comparable to those shown in Table 2.

Reviewer: 2

Reviewer Name: Dayeon Shin

Institution and Country: Department of Food Science and Human Nutrition,  
Michigan State University, East Lansing, MI, USA

Please state any competing interests or state 'None declared': None declared.

Comment:

The paper aimed to evaluate if prepregnancy BMI and pregnancy weight gain are associated with gestational hypertension and preeclampsia in Indonesian pregnant women. Although of potential interest to the readers of the journal, I have a number of concerns that I believe should be addressed.

Abstract

-Page 2, lines 8 & 39: Please be consistent using the terminology, "pregnancy weight gain" vs. "gestational weight gain" throughout the manuscript.

Response:

We thank the reviewer for the suggestion. The terminology "gestational weight gain" is now used throughout the manuscript.

Strengths and limitations of this study

-Page 3, Line 10: "Women were classified into the tertiles of their prepregnancy BMI" -> why is this one of the strengths of the study? Please find other strength of this research.

Response:

We do agree that this is not a strength and have left the statement out from the manuscript.

Introduction

-Page 4: Please add statements regarding why gestational hypertension and preeclampsia problem including long-term health consequences.

Response:

The statement about long-term health consequences of gestational hypertension and preeclampsia

has been added in the introduction, second paragraph.

Methods:

-Page 4, line 53-54: Explain what "socioeconomic background" is.

Response:

We used monthly family income, education, and women's employment status as proxies for socioeconomic background. We have accordingly revised this statement in the Methods section, second paragraph.

-Page 5, line 7: what are "previous complications and family history disease"? Please define them.

Response:

Previous complications refer to the women's history of pregnancy complications, while data about family history of diseases include family history of hypertension and type 2 diabetes. These sentences have now been modified to improve the clarity.

-Page 5, line 41: what is the difference between "confounding variables" vs. "intermediate variables"? The authors simply controlled for gestational weight gain in the "explanatory model". How is this different from the confounding variable?

Response:

The difference between confounding and intermediate variables lies in the interpretation of findings with their respective adjustments. In the present study, we a priori considered gestational weight gain as a possible intermediate variable in the relation between prepregnancy BMI and blood pressures in pregnancy. This was based on the premise that higher prepregnancy BMI likely causally determines (excessive) weight gain, and that (excessive) weight gain itself subsequently causes higher blood pressure in pregnancy. Therefore, gestational weight gain was thought to be in the causal pathway. If we suppose that gestational weight gain is indeed the intermediate variable in this association, adjustment for this variable would lead to an attenuated effect estimate between prepregnancy BMI and blood pressure. Confounding variables, in contrast, are variables external to the causal pathway that could cause bias if not adjusted for. We consider confounders variables that are somehow related to both prepregnancy BMI (determinant) and blood pressure in pregnancy (outcome), but not in the causal pathway. So while in principle, adjustment for confounders and intermediate variables may both change the association estimates, changes from adjustment for confounders will lead to interpretation of the estimates as not biased by such confounders, changes with adjustment for intermediate variables will lead us to conclude that these do indeed play a causal role in the chain of events.

-Page 6, line 6: were there any post-term births (>42 weeks)?

Response:

There were 85 women (4.2%) with post-term birth (birth at > 42 weeks after the estimated date of conception). We have added this in Table 1.

-Page 6, line 15: why did the authors divided prepregnancy BMI into tertiles? If previous literature recommended a lower cut-off for overweight/obesity in Asian population, how about dividing prepregnancy BMI into four categories based on "Asian criteria BMI cut-off points (Underweight: <18.5, normal weight: 18.5-22.9, overweight: 23.0-24.9, obese: >=25.0 kg/m<sup>2</sup>)?"

Response:

We do appreciate the reviewer's suggestion. However, in our etiologic study we aimed to show the relation between prepregnancy BMI and blood pressure irrespective of clinical cut off values. So while clinical cut off values are obviously very meaningful tools to drive clinical action, they do not in our view have special meaning in an analysis like ours. To maximize our statistical power we did perform the main analyses on a continuous basis (table 2) with regression coefficients interpreted as change in blood pressure per unit change in prepregnancy BMI. For further analyses (including graphics) we decided to classify women according to distribution-based cut off values, so both for reasons of presentation (group comparisons) and for ensuring sufficient statistical robustness. Although we are convinced about the findings, we do recognize that our cohort is still of limited total size and the suggested Asian-specific cut off values do lead to unequal group sizes, thus reducing statistical robustness.

#### Results & Discussion:

-Page 7, lines 29-32 & Page 10, line 36: "Prepregnancy weight gain did not mediate the effect of prepregnancy BMI on blood pressure level during pregnancy". How did the authors come with mediation effect? Please elaborate more results on Table 2 where the authors performed mixed linear regression such as coefficient between 1) prepregnancy BMI and blood pressure; 2) prepregnancy BMI and pregnancy weight gain; 3) prepregnancy weight gain and blood pressure. Without these results, it is not appropriate for the authors to conclude the mediation effect of prepregnancy weight gain between prepregnancy BMI and blood pressure level.

#### Response:

Here we also refer to our response to the reviewer above about the difference between confounding and intermediate variables. The component associations that the reviewer suggests to separately present, are intrinsic to our modeling. So our findings that the addition to the model of the intermediate variables did not change the association between prepregnancy BMI and blood pressure just means that the intermediate variable was not both related to prepregnancy BMI and to blood pressure. In other words, the intermediate variable can only change the association if it is related to both prepregnancy BMI and to blood pressure. Thus, the statement "Gestational weight gain did not mediate the effect of prepregnancy BMI on blood pressure level during pregnancy" was based on the finding of unchanged effect estimates after adjustment for gestational weight gain (effect estimates from the explanatory model vs the adjusted model). In our view, comparison between effect estimates from the two statistical models helps us evaluate if gestational weight gain is an intermediate variable. Although there is no formal objection to add the component associations, we do believe that it will complicate our manuscript. We prefer for that reason to keep table 2 as it is, but if the reviewer insists we are certainly willing to include them.

-Page 9, line 17: prepregnancy BMI is not a perfect measure of adiposity (women with higher muscles may have higher BMI compared to women with lower muscles with same weight). It is possible women with similar prepregnancy BMI have varying distribution of adipose tissue (Romero-Corral et al., 2008).

-Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)* 2008;32(6):959–966.

#### Response:

We fully agree that BMI may not be perfect in classifying adiposity, it is indeed an overall crude measure of the combination of lean body mass and body fat. The reviewer will agree that BMI is a proxy for body adiposity, as we had stated at the end of the Introduction section, and because the reviewer rightfully refers above to Asia specific clinical cut off values for prepregnancy BMI. The balance between lean body mass and body fat in relation to blood pressure in pregnancy is indeed

especially interesting, but beyond what we were able to study here. Referring to the suggested literature, we now added such statements to the discussion section.

-Page 10, line 12: spell out "HELLP syndrome".

Response:

An explanation about HELLP syndrome has been added to the text.

-Page 10, lines 44-47: The authors stated that excessive gestational weight gain is a determinant of gestational hypertension. Did the authors consider categorizing gestational weight gain into three groups based on the Institute of Medicine's recommendation: inadequate, adequate and excessive gestational weight gain and found the association between the excessive gestational weight gain and gestational hypertension and preeclampsia?

Response:

We thank reviewer for this comment. In the present study, we did not take gestational weight gain as determinant for gestational hypertension. Instead, we evaluated possible intermediate effect of gestational weight gain in the relation between prepregnancy BMI and gestational hypertension. We have revised the text to improve the clarity.

We also did not categorize women's gestational weight gain into the three groups (inadequate, adequate, and excessive weight gain). Referring to our responses above we analyzed gestational weight gain as a continuous variable to maximize the statistical power of our analyses.

-Page 11, line 53: see the previous comment regarding the "mediation effect" and revise the sentence "pregnancy weight gain does not appear to mediate these effects".

Response:

We hope in the above to have addressed the reviewer's concerns about our mediation analyses and therefore prefer not to revise the sentence.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Dayeon Shin Department of Food Science and Human Nutrition, Michigan State University, East Lansing, MI, USA
<b>REVIEW RETURNED</b>	17-Jun-2016

<b>GENERAL COMMENTS</b>	I read the manuscript with the authors' response through. I am happy with their response and all my concerns have been addressed. I would recommend that the manuscript should be accepted.
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