PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations of neonatal high birth weight with maternal pre-pregnancy body mass index and gestational weight gain: A case-control study in women from Chongqing, China
AUTHORS	Xie, Yao Jie; peng, rong; Han, Lingli; Zhou, Xiaoli; Xiong, Zhengai; Zhang, Yuan; Li, Junnan; Yao, Ruoxue; Li, Tingyu; Zhao, Yong

VERSION 1 - REVIEW

REVIEWER	Jumana Saleh College of Medicine and Health Sciences Sultan Qaboos University, Oman
REVIEW RETURNED	12-Jan-2016

GENERAL COMMENTS	This is a concise case-control study. Well written with a clear design and outcome. However, a few points are worth mentioning. Main comments: 1) The conclusion in the abstract, and page 14 in the discussion, was a overstatement as this was a case control association study, and not a cause- effect relation study. The quote "Our study confirms that excessive GWG....." need to be replaced by "The findings in this study suggest that excessive GWG....." 2) In the list of strengths and limitations of the study, the 3rd point is actually a strength in the study and not a limitations as it shows that the study outline was adhered to considering required exclusion criteria. 3) The aouthers need to expalain based on which international or national criteria was the BMI and GWG categorized. 4)In the discussion, page 12 the reference 32 is mentioned. It is important to mention some specifics considering the timing of that study, since the authors are actually mentioning that their data was collected before that study: By how long? 5) Several typos and grammar errors are found throughout the text: Page 4 under background 2nd line: In the recent 20 years Page 4 line 4: broad of health problems Line 11: after reference 24: "the risk of being HBW" need to be changed to "the risk of having a HBW outcome" Line 14: hispanic, western countries Line 16: change investigate more insight to : gain more insight last sentence: after reference 15: compared

	Page 6 in Methods: Line 2: mothers Line 3: pregnancies line 16: In total, 221 cases and 221 controls Page 7: Period of obtaining medical records Page 9: Under results second line: 10 controls quit (not quitted) Page 10: line 6: and gender of the newborns page 10: The line before the last line: but the association was not statistically... Page 13: Line 9, It is preferable to mention the word obese and not "fat".

REVIEWER	Gabriella Tikellis Murdoch Childrens Research Institute Australia
REVIEW RETURNED	19-Apr-2016

GENERAL COMMENTS	The paper examines the association between maternal pre-pregnancy BMI and gestational weight gain in mothers who delivered a baby of high birth weight. The findings have the potential to make an important contribution to the area of adiposity and birth weight in Asian populations but there are some issues that need to be addressed. Abstract The conclusions do not 'confirm' that excessive GWG increases risk of delivery of a HBW baby as many of the associations were underpowered. The wording should be toned done to align with the fact that a case-control study given its limitations can only examine associations. Methods 1) Were measures extracted from hospital medical records self-reported or actually measured? 2) As two methods for calculating gestational age were used, proportions of each should be reported and possible measurement biases should be considered in limitations in Discussion. 3) In the definitions of BMI categories, where would a BMI of 28.0 to 28.9 fit? 3) There is no indication of data on smoking or alcohol consumption being included. Is this due to the prevalence being very low or data not being available? This should be included in the Discussion. Results 1) Table 1: A breakdown of the numbers in each BMI category would be informative here. Consider incorporating the information in Table 3 into Table 1. 2) The gender difference between cases and controls should be explored further particularly as there is a greater proportion of male babies who are known to have a higher birth weight in general. Perhaps the matching should have done based on gender as well. 3) Most robust results from this study would be in Table 4 so perhaps focus on these when reporting. 4) Table 5: Most findings from this table should be interpreted with caution as the wide confidence intervals and the lower than expected ORs would suggest that the categories of both BMI and GWG have too small numbers and therefore the associations are driven by the excessive GWG and Normal weight groups respectively. Results should therefore be described as 'suggestive'.

	Discussion 1) The issue of maternal nutrition is not well discussed. This is an important determinant of birth weight which was not included in this study. The absence of such data should be included as a limitation 2) Discussion about the contrary findings of this study compared to most others should include whether differences may be due to this study being conducted in a different country, a different population with different access to healthcare and resources. 3) Limitations of the study are not adequately addressed. The broad use of words such as 'lifestyles' need to be defined in more detail. Other limitations which are inherent in a case-control design have not been mentioned.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jumana Saleh
Institution and Country: College of Medicine and Health Sciences, Sultan Qaboos University, Oman
Competing Interests: No competing interests are declared

This is a concise case-control study. Well written with a clear design and outcome. However, a few points are worth mentioning.

Main comments:

1) The conclusion in the abstract, and page 14 in the discussion, was a overstatement as this was a case control association study, and not a cause- effect relation study. The quote "Our study confirms that excessive GWG....." need to be replaced by "The findings in this study suggest that excessive GWG....."

Response: Thank you. We have revised the sentences accordingly:
Page 3: "…The findings in this study suggest that excessive GWG increases the risk of…"
Page 15: "…but suggests that excessive GWG increases…"

2) In the list of strengths and limitations of the study, the 3rd point is actually a strength in the study and not a limitations as it shows that the study outline was adhered to considering required exclusion criteria.

Response: Thank you for your comment. After consideration of two reviewers' comments, we revised these sentences as:
Page 15: "…In addition, some potential confounding factors, such as smoking and alcohol consumption during pregnancy, were not collected in the study. But we suggest that this deficiency would not overturn the findings. Because our study was adhered to considering required exclusion criteria."

3) The aouthers need to expalain based on which international or national criteria was the BMI and GWG categorized.

Response: The standard for categorizing pre-pregnancy BMI was from the Chinese maternal pre-pregnancy BMI category criteria; the three GWG statuses and the corresponding weight gain ranges were based on the 2009 IOM GWG recommendations. We have clarified these contents in the manuscript:
Page 7: "…According to the Chinese maternal pre-pregnancy BMI status [30], the pre-pregnancy BMI

was categorized to…"; "…Based on the 2009 IOM GWG recommendations [31], GWG was defined as…"

4) In the discussion, page 12 the reference 32 is mentioned. It is important to mention some specifics considering the timing of that study, since the authors are actually mentioning that their data was collected before that study: By how long?

Response: We checked back the time of data collection in that reference, the data in their study were collected in 2012. Our data collection was conducted from 2010 to 2012. It cannot be considered as a long time lag. We thereby reconsidered the reason of GWG discrepancy in these two studies. Actually women in our study lived in Chongqing, a southwest city in remote area of China, while in that study almost all the women lived in Beijing, the capital of China. We think the living conditions, as well as the nutrition statuses are different between these two cities. We have now revised the explanation in the discussion section:
Page 12: "…it was lower than a recent publication which indicated an average weight gain of 16.2 kg in same BMI category in women lived in Beijing [32]. Chongqing is a southwest city of China, while Beijing is the capital. This finding is consistent with previous study [15] that women lived in remote area of China had relative lower GWG, which reflecting the discrepancy of living conditions and nutrition statuses in different areas of China."

5) Several typos and grammar errors are found throughout the text:

Response: Thank you for your comments. We have corrected the typos and grammar errors.

Page 4 under background
2nd line: In the recent 20 years
Done
Page 4 line 4: broad of health problems
Done
Line 11: after reference 24: "the risk of being HBW" need to be changed to "the risk of having a HBW outcome"
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Page 13: Line 9, It is preferable to mention the word obese and not "fat".
Done

Reviewer: 2
Reviewer Name: Gabriella Tikellis
Institution and Country: Murdoch Childrens Research Institute, Australia
Competing Interests: None declared

The paper examines the association between maternal pre-pregnancy BMI and gestational weight gain in mothers who delivered a baby of high birth weight.
The findings have the potential to make an important contribution to the area of adiposity and birth weight in Asian populations but there are some issues that need to be addressed.
Abstract
The conclusions do not 'confirm' that excessive GWG increases risk of delivery of a HBW baby as many of the associations were underpowered. The wording should be toned done to align with the fact that a case-control study given its limitations can only examine associations.

Response: Thank you. We have revised the sentences accordingly.
Page 3: "…The findings in this study suggest that excessive GWG increases the risk of…"

Methods
1) Were measures extracted from hospital medical records self-reported or actually measured?

Response: The measures extracted from hospital medical records were all actually measured. We have modified the sentences in the method section:
Page 7: "Mother's age (identified from identity card), height, pre-pregnancy body weight, body weight at delivery, and the reproductive characteristics (gravidity, parity, mode of delivery, prenatal genetic diseases, pregnancy duration, frequency of prenatal examination, blood pressure, pregnancy complications), as well as the newborns' information including birth weight, birth length, gender and gestational age were all extracted from participants' hospital medical records. These variables were objectively measured by professional healthcare staffs."

2) As two methods for calculating gestational age were used, proportions of each should be reported and possible measurement biases should be considered in limitations in Discussion.

Response: we have now added this information in the first paragraph of the Result section:
Page 9: "…Around 45% (199/442) participants' gestational age was determined by the dating ultrasound scan. This proportion was similar in cases and controls (44.3% vs. 45.7%, P>0.05)."
Also, the possible bias was described in the Discussion section:
Page 15: "…Secondly, we used two methods for calculating gestational age. This might lead to certain measurement bias. But we suggest that its influence on main results was negligible, because comprehensive adjustment (including adjustment for gestational age) was adopted in subsequent regression analysis. Nevertheless, consistent measurement for gestational age is suggested in future studies."

3) In the definitions of BMI categories, where would a BMI of 28.0 to 28.9 fit?

Response: Thanks for pointing out such error in the manuscript. Actually the cut-off point for pre-pregnancy obesity is BMI ≥ 28 kg/m2 according to Chinese standard. We have revised it in the

manuscript (page 7).

3) There is no indication of data on smoking or alcohol consumption being included. Is this due to the prevalence being very low or data not being available? This should be included in the Discussion.

Response: We have now replaced the word “lifestyles” as “smoking and alcohol consumption” in the manuscript. We didn’t collect the data of smoking and drinking due to data was not being available. We have revised the corresponding sentences in the manuscript:
Page 15: “…Finally, some potential confounding factors, such as smoking and alcohol consumption during pregnancy, were not collected in the study.”

Results
1) Table 1: A breakdown of the numbers in each BMI category would be informative here. Consider incorporating the information in Table 3 into Table 1.

Response: We have considered illustrating the breakdown numbers in each BMI/GWG category in the Table 1. However, more columns should be added only for this variable, the structure of the Table 1 would become a little bit confusing. We thereby demonstrated this information in a separated Table (the Table 3).

2) The gender difference between cases and controls should be explored further particularly as there is a greater proportion of male babies who are known to have a higher birth weight in general. Perhaps the matching should have done based on gender as well.

Response: Yes, the proportions of male/female babies were different in cases and controls. However, we suggest that the possible gender-induced bias was negligible because gender was adjusted in the logistic regression model. Nevertheless, it was indeed a limitation of the study. We have now described this limitation in the discussion section:
Page 15: “In our study, no gender-matched design (compared with controls, cases had more male babies) is a limitation in the aspect of selection of a comparable control group.”

3) Most robust results from this study would be in Table 4 so perhaps focus on these when reporting.

Response: We agree that Table 4 is the important table which shows the major findings of the study. We elaborated the results and discuss the findings from this table in different sections of the manuscript. Such as:
Page 10: “The ORs of being HBW by one unit increase in pre-pregnancy BMI and GWG were shown in Table 4. The crude odds was 16% greater with each kg of GWG (OR: 1.16, 95% CI: 1.10 - 1.21, P<0.001)…they were adjusted in the model as confounders…In the stratified models by pre-pregnancy BMI status, a strengthened association between GWG and HBW was found among pre-pregnancy normal weight women... But the associations were no statistically significant among pre-pregnancy underweight, overweight and obese women (both P>0.05).”
Page 12: “…We found a positive relationship between GWG and HBW, in which higher weight gain during pregnancy led to higher risk of delivery of HBW babies…However, we did not observe a significant association between pre-pregnancy BMI and HBW…”
Page 13: “…Findings from logistic regression analysis indicated that GWG had significant effect on neonatal birth weight, higher GWG was associated with higher risk of HBW. This was consistent with many previous studies [15, 37-39]…”
Page 13: “…Nevertheless, the significant association between GWG and HBW across all pre-pregnancy BMI range suggesting that reasonable weight gain is notable important during pregnancy, regardless of the women are thin, obese, or normal weight at the pre-pregnancy period.”

4) Table 5: Most findings from this table should be interpreted with caution as the wide confidence intervals and the lower than expected ORs would suggest that the categories of both BMI and GWG have too small numbers and therefore the associations are driven by the excessive GWG and Normal weight groups respectively. Results should therefore be described as 'suggestive'.

Response: Thank you for your comment. We have modified the descriptions for Table 5 in the manuscript:
Page 11: "Table 5 shows the ORs of being HBW for different categories of pre-pregnancy BMI and GWG, respectively; and for GWG subgroups among pre-pregnancy normal weight mothers."
Page 11: "…the adjusted odds was 10.3 times greater compared with appropriate GWG mothers (adjusted OR: 10.27; P<0.001) with a wide confidence interval of 3.20 to 32.95."
Page 13: "…In our study, pre-pregnancy normal weight women with excessive GWG had high odds of having HBW babies, suggesting average-sized women shall pay more attention to avoid over nutrition during pregnancy."

Discussion
1) The issue of maternal nutrition is not well discussed. This is an important determinant of birth weight which was not included in this study. The absence of such data should be included as a limitation

Response: We have now added the limitation of absence of maternal nutrition data in the Discussion section:
Page 15: "…Thirdly, maternal nutrition data were absence in the study. Maternal nutrition status is strongly associated with pre-pregnancy BMI and GWG. More detailed information in this aspect could help in better elaboration of the results."

2) Discussion about the contrary findings of this study compared to most others should include whether differences may be due to this study being conducted in a different country, a different population with different access to healthcare and resources.

Response: We have added the explanation in the Discussion section:
Page 13: "…It might be due to this study being conducted in a remote area of China, a different population with different access to healthcare and resources."

3) Limitations of the study are not adequately addressed. The broad use of words such as 'lifestyles' need to be defined in more detail. Other limitations which are inherent in a case-control design have not been mentioned.

Response: We have changed the word "lifestyles" to "smoking and alcohol consumption during pregnancy". And the limitation part has been revised thoroughly:
Page 15: "In our study, no gender-matched design (compared with controls, cases had more male babies) is a limitation in the aspect of selection of a comparable control group. Despite any common limitations inherent in the case-control study, there are also some particular limitations in our study. Firstly, because of the small sample of pre-pregnancy overweight and obese participants, we could not calculate OR for each GWG subgroup. Secondly, we used two methods for calculating gestational age. This might lead to certain measurement bias. But we suggest that its influence on main results was negligible, because comprehensive adjustment (including adjustment for gestational age) was adopted in subsequent regression analysis. Nevertheless, consistent measurement for gestational age is suggested in future studies. Thirdly, maternal nutrition data were absence in the study. Maternal nutrition status is strongly associated with pre-pregnancy BMI and GWG. More detailed information in this aspect could help in better elaboration of the results. In addition, some potential confounding factors, such as smoking and alcohol consumption during pregnancy, were not collected

in the study. But we suggest that this deficiency would not overturn the findings. Because our study was adhered to considering required exclusion criteria."