

## PEER REVIEW HISTORY

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## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association between vomiting in the first trimester and preterm birth: a retrospective birth cohort study in Wuhan, China
<b>AUTHORS</b>	Hu, Ronghua; Chen, Yawen; Zhang, Yiming; Qian, Zhengmin; Liu, Yan; Vaughn, MG; Xu, Shunqing; Zheng, Tongzhang; Liu, Mingzhu; Zhang, Bin

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Chew Kah Teik Universiti Kebangsaan Malaysia Medical Center, Malaysia
<b>REVIEW RETURNED</b>	23-Apr-2017

<b>GENERAL COMMENTS</b>	<p>This is an interesting study with large sample size. However, there are many aspects need to be revised.</p> <ol style="list-style-type: none"><li>1. The study design is supposed to be a retrospective study. It is not a prospective cohort study as described in the title. Author(s) should clarify this as it causes confusion to readers.</li><li>2. In the methodology:<ol style="list-style-type: none"><li>a) Can author(s) please explain why samples of maternal age less than 15 and more than 50 were excluded?</li><li>b) Any particular reasons why the symptom of vomiting was divided in such categories – less than 3 times and &gt; 3 times?</li></ol></li><li>3. In table 1, author(s) should put in statistical analysis of p value, to indicate whether each variable is statistically significant or not.</li><li>4. Can the author(s) include a table to show the characteristic or demographic data of women with vomiting in early pregnancy and its association with preterm birth? Table 1 alone just reflected the general sample comparing preterm birth and term birth. How about those women with vomiting? What is the number or percentage of preterm birth in keeping with the variables author described?</li><li>5. Can the author(s) explain why pre-pregnancy BMI was chosen as variable rather than weight gained in pregnancy?</li><li>6. Author(s) should discuss in detail regarding the influence of different variables (age, education level etc) in keeping with the association of vomiting in early pregnancy and preterm birth.</li><li>7. There are many grammatical errors in the manuscript.</li></ol>
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<b>REVIEWER</b>	Ewelina Rogozinska Barts and The London School of Medicine and Dentistry, Queen Mary University of London United Kingdom
<b>REVIEW RETURNED</b>	19-May-2017

<b>GENERAL COMMENTS</b>	<p>Hu et al. manuscript is well written and coherent piece of research; however, I have a few concerns and comments:</p> <p><b>Abstract</b> Setting: "Pregnant women living in Wuhan, China" this is description of population, not the setting.</p> <p><b>Methods</b> Variables, second paragraph. The meaning of BMI has been already explained earlier on in the text.</p> <p>Why the authors haven't investigated the interaction between the women's BMI and the effect rather than performing only a subgroup analysis?</p> <p>Why the authors did not adjust for weight gain in pregnancy? There is some evidence suggesting that insufficient weight gain in pregnancy, especially among underweight and women with healthy weight, may increase the odds of premature delivery.</p> <p><b>Result</b> Why in the text the authors use the term relative risk but the headings of Table 2 have OR for the same values of effect estimate? Also the abbreviation in the table is not explained.</p> <p><b>Discussion</b> Second paragraph - I don't feel that the term 'likelihood' has been used here in a correct way. The sentence should be revised to something like: "... the study has found an association between first trimester vomiting and preterm birth before 37 weeks of gestation."</p> <p>Finally, I could not see the STROBE checklist attached to the submission, and the manuscript requires some additional editorial work including unifying the reference style.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. The study design is supposed to be a retrospective study. It is not a prospective cohort study as described in the title. Author(s) should clarify this as it causes confusion to readers.

Authors' response: We greatly appreciate the reviewer's important comment. We have changed "prospective" into "retrospective" in our title, abstract, and study population sections.

2. In the methodology:

a) Can author(s) please explain why samples of maternal age less than 15 and more than 50 were excluded?

Authors' response: Many thanks for review's comments. In China, the reproductive age of women recommended by the Ministry of Health recommend is 15~49. We could not check the information of

women aged less than 15 and more than 50 years old. In order to avoid incorrect information of those women, we excluded those women aged less than 15 and more than 50 years old.

b) Any particular reasons why the symptom of vomiting was divided in such categories – less than 3 times and > 3 times?

Authors' response: In our study, vomiting was dichotomized into yes and no response variables.

3. In table 1, author(s) should put in statistical analysis of p value, to indicate whether each variable is statistically significant or not.

Authors' response: We greatly appreciate the reviewer's important comment. We have added the p values for each variable in Table 1.

4. Can the author(s) include a table to show the characteristic or demographic data of women with vomiting in early pregnancy and its association with preterm birth? Table 1 alone just reflected the general sample comparing preterm birth and term birth. How about those women with vomiting? What is the number or percentage of preterm birth in keeping with the variables author described?

Authors' response: We greatly appreciate the reviewer's important comment. We have added data of women with vomiting in early pregnancy and its relationships associated with preterm birth in Table 1.

5. Can the author(s) explain why pre-pregnancy BMI was chosen as variable rather than weight gained in pregnancy?

Authors' response: Total gestational weight gain (GWG) was calculated by subtracting pre-pregnancy weight from the weight on delivery day. The Institute of Medicine (2009) recommended GWG according to pre-pregnancy BMI defining as 18.5 kg/m<sup>2</sup> (underweight), 18.5~24.9 kg/m<sup>2</sup> (normal), 25.0~29.9 kg/m<sup>2</sup> (overweight) and ≥30.0 kg/m<sup>2</sup> (obese) (Weight Gain During Pregnancy: Reexamining the Guidelines: National Academies Press. 2009). In our manuscript, pre-pregnancy BMI was categorized into four groups that are standard in China: 18.5 kg/m<sup>2</sup> (underweight), 18.5~23.9 kg/m<sup>2</sup> (normal), 24.0~27.9 kg/m<sup>2</sup> (overweight) and ≥28.0 kg/m<sup>2</sup> (obese) (Is China facing an obesity epidemic and the consequences? The trends in obesity and chronic disease in China. International journal of obesity (2005) 2007;31(1):177-88 doi: 10.1038/sj.ijo.0803354[published Online First: Epub Date]), which were different in overweight and obese groups according to the Institute of Medicine categorizations. Therefore, we did not find suitable recommendations for GWG in Chinese population. Additionally, pre-pregnancy BMI has been investigated as a factor contributing to preterm birth in several studies (Overweight and obesity in mothers and risk of preterm birth and low birth weight infants: systematic review and meta-analyses. BMJ (Clinical Research Ed.) 2010;341:c3428). Thus, we chose pre-pregnancy BMI as variable rather than weight gained in pregnancy.

6. Author(s) should discuss in detail regarding the influence of different variables (age, education level etc) in keeping with the association of vomiting in early pregnancy and preterm birth.

Authors' response: We greatly appreciate the reviewer's important comment.

We have added one paragraph "Our results showed that socio-demographic factors, such as age, education level, parity, and gravidity, might influence PTB. Previous studies have indicated that women with advanced maternal age were associated with increased risk of PTB (Advanced maternal age and pregnancy outcomes: a multicountry assessment. BJOG : an international journal of obstetrics and gynaecology 2014;121 Suppl 1:49-56 doi: 10.1111/1471-0528.12659[published Online First: Epub Date]); Association between preterm birth and its subtypes and maternal sociodemographic characteristics during the post-transitional phase in a developing country with a very high human development index. Public health 2017;147:39-46 doi: 10.1016/j.puhe.2017.01.027[published Online First: Epub Date]). Araya BM et al. reported that age >35 years, delivery of more than two fetuses, and <8 years of education were risks factors for PTB (Association between preterm birth and its subtypes and maternal sociodemographic characteristics during the post-transitional phase in a developing country with a very high human development index. Public health 2017;147:39-46 doi: 10.1016/j.puhe.2017.01.027[published Online First: Epub Date]).

Women aged >35 had longer exposure times to chronic pathologies and unhealthy lifestyles (Association of elevated free fatty acids during late pregnancy with preterm delivery. *Obstetrics and gynecology* 2008;112(2 Pt 1):297-303 doi: 10.1097/AOG.0b013e3181802150[published Online First: Epub Date]), and higher prevalence of maternal obesity in older mothers, which were associated with risks factors for PTB (Brazilian multicentre study on preterm birth (EMIP): prevalence and factors associated with spontaneous preterm birth. *PloS one* 2014;9(10):e109069 doi: 10.1371/journal.pone.0109069[published Online First: Epub Date]). Several studies demonstrated that the lower the socio-economic and education level, the higher the probability of developing infection, and that was clearly associated with PTB before 30 weeks of gestation ([Risk factors for preterm deliveries in a public hospital]. *Revista medica de Chile* 2012;140(1):19-29 doi: /S0034-98872012000100003[published Online First: Epub Date]; Epidemiology and causes of preterm birth. *Lancet* 2008;371(9606):75-84 doi: 10.1016/S0140-6736(08)60074-4[published Online First: Epub Date]).” in discussion section.

7. There are many grammatical errors in the manuscript.

Authors' response: We greatly appreciate the reviewer's important comment. We have carefully checked our manuscript.

Reviewer: 2

1. Abstract

Setting: "Pregnant women living in Wuhan, China" this is description of population, not the setting.

Authors' response: We greatly appreciate the reviewer's important comment. We have changed the setting in "Wuhan, a central city of China." in abstract.

2. Methods

(1) Variables, second paragraph. The meaning of BMI has been already explained earlier on in the text.

Authors' response: We greatly appreciate the reviewer's important comment. We have deleted the explanation of BMI in the second paragraph of variables section.

(2) Why the authors haven't investigated the interaction between the women's BMI and the effect rather than performing only a subgroup analysis?

Authors' response: In the exploratory analysis, we found that there was not a statistical significant interaction between the women's pregnancy BMI and vomiting in the first trimester for PTB ( $P=0.6618$ ). Additionally, the percent concordant increased 15.3% when pregnancy BMI was included in our model, which indicated that pregnancy BMI was a confounder for investigating the association between vomiting in the first trimester and PTB. Therefore, we performed a subgroup analysis rather than investigated the interaction between the women's pregnancy BMI and the effect.

(3) Why the authors did not adjust for weight gain in pregnancy?

There is some evidence suggesting that insufficient weight gain in pregnancy, especially among underweight and women with healthy weight, may increase the odds of premature delivery.

Authors' response: Total gestational weight gain (GWG) was calculated by subtracting pre-pregnancy weight from the weight on delivery day. The Institute of Medicine (2009) recommended GWG according to pre-pregnancy BMI defining as 18.5 kg/m<sup>2</sup> (underweight), 18.5~24.9 kg/m<sup>2</sup> (normal), 25.0~29.9 kg/m<sup>2</sup> (overweight) and  $\geq 30.0$  kg/m<sup>2</sup> (obese) (Weight Gain During Pregnancy: Reexamining the Guidelines: National Academies Press. 2009). In our manuscript, pre-pregnancy BMI was categorized into four groups that are standard in China: 18.5 kg/m<sup>2</sup> (underweight), 18.5~23.9 kg/m<sup>2</sup> (normal), 24.0~27.9 kg/m<sup>2</sup> (overweight) and  $\geq 28.0$  kg/m<sup>2</sup> (obese) (Is China facing an obesity epidemic and the consequences? The trends in obesity and chronic disease in China. *International journal of obesity* (2005) 2007;31(1):177-88 doi: 10.1038/sj.ijo.0803354[published Online First: Epub Date]), which were different in overweight and obese groups according to the Institute of Medicine categorizations. Therefore, we did not find suitable recommendations for GWG in Chinese

population.

### 3. Result

Why in the text the authors use the term relative risk but the headings of Table 2 have OR for the same values of effect estimate? Also the abbreviation in the table is not explained.

Authors' response: We greatly appreciate the reviewer's important comment. We have changed "OR" into "RR" and added the abbreviations in Table 2.

### 4. Discussion

Second paragraph - I don't feel that the term 'likelihood' has been used here in a correct way. The sentence should be revised to something like: "... the study has found an association between first trimester vomiting and preterm birth before 37 weeks of gestation."

Authors' response: We greatly appreciate the reviewer's important comment. We have revised the sentence into "we have found an association between vomiting in the first trimester and PTB before 37 weeks of gestation."

5. Finally, I could not see the STROBE checklist attached to the submission, and the manuscript requires some additional editorial work including unifying the reference style.

Authors' response: We have uploaded the STROBE checklist attached the revision submission, and we have used EndNote software to manage references.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Ewelina Rogozinska Barts and The London School of Medicine and Dentistry Queen Mary University of London
<b>REVIEW RETURNED</b>	26-Jun-2017

<b>GENERAL COMMENTS</b>	<p>I have carefully reviewed the revised manuscript, and have further comments and concerns mainly regarding the description of the methods and the findings.</p> <p>Major comments</p> <p>In the aims of their work, the authors specify they want to assess whether pre-pregnancy BMI modifies the association between 1st trim vomiting and the risk of preterm delivery. However, nowhere in the description of their statistical analysis can be found how the 'modification' has been assessed and in their conclusions, they state that women with underweight and normal pre-pregnancy BMI that experienced vomiting are more likely to have a PTB.</p> <p>In their response, the authors admit that in the exploratory analysis they did check for subgroup difference and the modifying effect of BMI was not statistically significant. This is an important information that should be provided in the manuscript for the better interpretation and understanding of presented findings, yet not given in the manuscript.</p> <p>The Relative Risk does not seem to be a suitable measure in this study due to the participants sampling method.</p> <p>Table 1 How did the authors test this? There is no information in the methods section on how the difference in women characteristics was compared. One cannot provide a p-value without explaining how</p>
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	<p>was it obtained.</p> <p>Minor comments use of term 'obstetric nurse' - do the authors mean midwife?</p> <p>Maternal age was categorised into 3 groups: younger than 25, 25~34 years old, and 35 years old and older.” Why was the age variable not kept continuous? What is the rationale behind splitting this into 3 categories and what is the rationale behind presented cut-offs?</p> <p>Finally, I am afraid I don't understand authors' response to my query regarding gestation weight gain. Provided reply does not explain why authors did not consider gestational weight gain as a confounder in their analysis.</p>
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## VERSION 2 – AUTHOR RESPONSE

### Major comments

1. In the aims of their work, the authors specify they want to assess whether pre-pregnancy BMI modifies the association between 1st trim vomiting and the risk of preterm delivery. However, nowhere in the description of their statistical analysis can be found how the 'modification' has been assessed and in their conclusions, they state that women with underweight and normal pre-pregnancy BMI that experienced vomiting are more likely to have a PTB.

Authors' response: We greatly appreciate the reviewer's important comment. The confounders modified in our stratified analysis included maternal age, education, parity, gravidity, and offspring sex. Now we have added this in the statistical analysis section.

2. In their response, the authors admit that in the exploratory analysis they did check for subgroup difference and the modifying effect of BMI was not statistically significant. This is an important information that should be provided in the manuscript for the better interpretation and understanding of presented findings, yet not given in the manuscript.

Authors' response: In our exploratory analysis, we found that there was not a statistical significant interaction of the women's pre-pregnancy BMI and vomiting in the first trimester on pre-term birth (PTB) ( $P=0.6618$ ). There was a significant difference between different pre-pregnancy BMI groups and PTB (Table1). The purpose of the present study was to explore the association between vomiting in the first trimester and PTB. In the previous reply letter, the percent concordant increased 15.3% when pre-pregnancy BMI was included in the model. Shaw et al.

found that maternal pre-pregnancy BMI was associated with PTB risk (Shaw GM, Wise PH, Mayo J, et al. Maternal prepregnancy body mass index and risk of spontaneous preterm birth. Paediatric and perinatal epidemiology 2014;28(4):302-11 doi: 10.1111/ppe.12125). Pregnancy BMI was considered as a confounder and we have performed a subgroup analysis based pre-pregnancy BMI to investigate the association between vomiting in the first trimester and PTB. In order to provide a better interpretation and understanding of our findings, we have provided the analysis results of association between women and infants' characteristics and PTB in supplement table. Now, we have added "Additionally, we assessed the associations of maternal age, education, parity, gravidity, pre-pregnancy BMI, and offspring sex with risk of PTB. PTB was associated with all of the evaluated exposures (Table S1)." in our results section.

3. The Relative Risk does not seem to be a suitable measure in this study due to the participants sampling method.

Authors' response: Many thanks for reviewer's comments. We have changed "Relative Risk" into

“Odds Ratio” in the revised manuscript.

4. Table 1 How did the authors test this? There is no information in the methods section on how the difference in women characteristics was compared. One cannot provide a p-value without explaining how was it obtained.

Authors' response: We greatly appreciate the reviewer's important comment. P-values were estimated by Chi-square tests, and we have made change according in the statistical analysis section.

Minor comments

5. use of term 'obstetric nurse' - do the authors mean midwife?

Authors' response: Yes, “obstetric nurse” in our manuscript means midwife. We have changed “obstetric nurse” into “midwife” for better understanding in our materials and methods sections.

6. Maternal age was categorised into 3 groups: younger than 25, 25~34 years old, and 35 years old and older.” Why was the age variable not kept continuous? What is the rationale behind splitting this into 3 categories and what is the rationale behind presented cut-offs?

Authors' response: We greatly appreciate the reviewer's important comment. Given that the influence of advanced maternal age on preterm birth could not be evaluated and adjusted if the age was continuous variable, we categorized maternal age into groups. Advanced maternal age is generally defined as pregnancy in women aged 35 years or older, and it was proved a risk factor for PTB (Laopaiboon M, Lumbiganon P, Intarut N, et al. Advanced maternal age and pregnancy outcomes: a multicountry assessment. BJOG : an international journal of obstetrics and gynaecology 2014;121 Suppl 1:49-56 doi: 10.1111/1471-0528.12659). The cut-offs referred to one previous study, which split maternal age into younger than 20, 20~34 years old, and 35 years old and older (Araya BM, Diaz M, Paredes D, Ortiz J. Association between preterm birth and its subtypes and maternal sociodemographic characteristics during the post-transitional phase in a developing country with a very high human development index. Public health 2017;147:39-46 doi: 10.1016/j.puhe.2017.01.027). However, the proportion of women aged younger than 20 were too low (1.5%), to provide a stable analysis results, We categorized maternal age into 3 groups: younger than 25, 25~34 years old, and 35 years old and older.

7. Finally, I am afraid I don't understand authors' response to my query regarding gestation weight gain. Provided reply does not explain why authors did not consider gestational weight gain as a confounder in their analysis.

Authors' response: Bodnar et al. demonstrated that studies linking total gestation weight gain (GWG) to adverse pregnancy outcomes such as preterm birth may therefore be biased (Bodnar LM, Pugh SJ, Abrams B, Himes KP, Hutcheon JA.

Gestational weight gain in twin pregnancies and maternal and child health: a systematic review. Journal of perinatology : official journal of the California Perinatal Association 2014;34(4):252-63 doi: 10.1038/jp.2013.177), and the Nutrition During Pregnancy Committee advised that GWG should be set according to pre-pregnancy BMI back in 1990 (Institute of Medicine (IOM). Nutrition during Pregnancy: Part I, Weight Gain: Part II, Nutrient Supplements. Washington (DC): National Academies Press (US); 1990). However, there is no recommended GWG taking into account the pre-pregnancy BMI classification for Asian. In our further research, we will explore the recommended GWG according to the pre-pregnancy BMI for Chinese adults.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Ewelina Rogozinska Queen Mary University of London Barts and The London School of Medicine and Dentistry The United Kingdom
<b>REVIEW RETURNED</b>	11-Aug-2017

<b>GENERAL COMMENTS</b>	Abstract Setting: primary care, tertiary unit?; please specify Main text Table 2 provides estimates for OR with three decimal places while the supplementary Table 1 with only two; please unify
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### VERSION 3 – AUTHOR RESPONSE

Abstract

Setting: primary care, tertiary unit?; please specify

Authors' response: In the abstract section, the setting was "Wuhan, a central city of China".

Main text

Table 2 provides estimates for OR with three decimal places while the supplementary Table 1 with only two; please unify.

Authors' response: We greatly appreciate the reviewer's important comment. We have changed ORs (Table 2) into two decimal places.