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Association between vomiting in the first trimester and preterm birth: a retrospective birth cohort study in Wuhan, China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017309.R1
Article Type:	Research
Date Submitted by the Author:	07-Jun-2017
Complete List of Authors:	Hu, Ronghua; Wuhan Medical and Healthcare Center for Women and Children Chen, Yawen; Wuhan Medical and Healthcare Center for Women and Children, Zhang, Yiming; Wuhan Medical and Healthcare Center for Women and Children Qian, Zhengmin ; Saint Louis University, Department of Epidemiology, School of Public Health Liu, Yan; Wuhan Medical and Healthcare Center for Women and Children Vaughn, MG; Saint Louis University, School of Social Work Xu, Shunqing; Tongji Medical College, Huazhong University of Science and Technology, Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health, School of Public Health Zheng, Tongzhang; Brown University, Department of Epidemiology, School of Public Health Liu, Mingzhu; Wuhan Medical and Healthcare Center for Women and Children Zhang, Bin; Wuhan Medical and Healthcare Center for Women and Children
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	PRETERM BIRTH, Cohort study, pre-pregnancy body mass index, vomiting

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Manuscripts

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4 **Association between vomiting in the first trimester and preterm birth:**
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6 **a retrospective birth cohort study in Wuhan, China**
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8 Ronghua Hu^{1§}, Yawen Chen^{1§}, Yiming Zhang¹, Zhengmin Qian², Yan Liu¹, Michael
9 G. Vaughn², Shunqing Xu³, Tongzhang Zheng⁴, Mingzhu Liu¹, Bin Zhang^{1*}
10
11
12

13 ¹ Wuhan Medical and Healthcare Center for Women and Children, Wuhan, Hubei,
14 People's Republic of China
15
16

17 ² Department of Epidemiology, College for Public Health and Social Justice, Saint
18 Louis University, MO, United States of America
19
20
21

22 ³ Key Laboratory of Environment and Health, School of Public Health, Tongji
23 Medical College, Huazhong University of Science and Technology, Wuhan, Hubei,
24 People's Republic of China
25
26
27
28

29 ⁴ Department of Epidemiology, School of Public Health, Providence, Brown
30 University, RI, United States of America
31
32
33

34 [§]These authors contributed equally to this work
35
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37

38 ***Corresponding author**
39

40 Full name: Bin Zhang
41
42

43 Postal address: No.100 Hongkong Road, Wuhan 430014, Hubei, China,
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46 E-mail: mchwhzb@163.com
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49 Telephone and fax number: +86-027-82433149
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Abstract

Objective: Although vomiting in the first trimester has been reported to be associated with preterm birth (PTB), findings supporting this association remain inconsistent. Our aim was to assess the association between vomiting and PTB, as well as evaluate if the association is modified by pre-pregnancy body mass index (BMI).

Design: A retrospective cohort study.

Setting: Wuhan, a central city of China.

Participants: A total of 317,463 pregnant women who had a live, singleton newborn from January 1, 2010, to May 23, 2016 were enrolled in our study.

Main outcome measure: PTB was defined as gestational age <37 gestational weeks. Gestational age was calculated using reports from mothers based on the first day of their last menstrual period. An ultrasound was routinely used to determine gestational age before 12 gestational weeks.

Results: Of the 317,463 pregnant women, 29.88% (94,857) experienced vomiting in the first trimester and 5.00% (15,889) experienced a PTB. Vomiting in the first trimester increased the risk for PTB and the multivariable adjusted relative risk (RR) was 1.05 (95% confidence interval (CI) = 1.02~1.09). In the stratified analyses, the association of vomiting in the first trimester was significant among underweight women (adjusted RR=1.08, 95%CI=1.04~1.17) and normal pre-pregnancy BMI women (adjusted RR=1.06, 95%CI=1.02~1.11), but not in overweight women (adjusted RR=1.01, 95% CI=0.90~1.14) and obese women (adjusted RR=0.93, 95% CI=0.73~1.19).

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4 **Conclusions:** Our study indicates that vomiting in the first trimester was associated
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6 with PTB. Additionally, women with underweight and normal pre-pregnancy BMI
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8 that experienced vomiting are more likely to have a PTB.
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11 **Keywords:** vomiting; preterm birth; pre-pregnancy body mass index
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14 15 16 **Strengths and limitations of this study** 17

- 18 1. The present study is a cohort study enrolled a large population of 317,463 pregnant
19 women.
20
21
- 22 2. This is the first study exploring the relationship between vomiting in the first
23 trimester and PTB in Chinese women by pre-pregnancy BMI status.
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- 26 3. Vomiting symptoms was based on self-reported, which may be a possible source of
27 bias.
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- 30 4. The prevalence of overweight and obesity were relatively low in our sample, and
31 the relationship between vomiting and PTB in women with a high pre-pregnancy BMI
32 needs to be further assessed.
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Introduction

Nausea and vomiting in pregnancy (NVP) is a collection of symptoms composed of nausea alone, or nausea in combination with vomiting.[1] This condition typically starts prior to 9 weeks of gestation and subsides by the end of the first trimester; however, this condition has been shown to continue into the second trimester in up to 25% of pregnant women and for 0.3-2.3% into the third trimester.[2] NVP has an important effect on both individuals and society as it causes emotional distress, depression, and can have a negative effect on a woman's activities and relationships.[3 4] NVP also has been found to lead to loss of time at work and a decrease in job productivity.[5] The etiology of NVP remains unknown, although it is currently believed to be related to early pregnancy hormones.[6]

Almost 70% of women worldwide experience NVP.[7] The average rate of vomiting only in early pregnancy is 47.1%, and the reported rates generally range from 22.3% to 63.5%.[8] A Norwegian cohort investigation reported that the rate of NVP was 33% among 51,675 women.[9] Källén et al. studied the occurrence of NVP via questionnaires in 3,675 Swedish pregnant women and observed that 38.3% of pregnant women reported vomiting in early pregnancy.[10] One previous meta-analysis, which included 23 studies comprised of 67,602 women,[11] estimated the rate of NVP in the USA to be as high as 68.6%. Meanwhile, studies on the rate of NVP in China are few and are limited by their small sample sizes. Chin et al.[12] conducted a study in a district hospital in Hong Kong in 1989 and found that the incidence of NVP was 74.9% among 1,453 patients. Another cross-sectional study

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4 conducted in a University obstetric unit in Hong Kong revealed that the prevalence of
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6 NVP was 90.9% among 396 women.[13]
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9 In previous studies, NVP was not found to be associated with primary maternal
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11 diseases such as gastrointestinal infections or allergies.[8] Recently there was a
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13 resurgence of interest in topics related to NVP, such as death,[14] pregnancy
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15 complications,[15] and birth outcomes.[16] Some studies reported that women with
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17 NVP were more likely to have a preterm birth (PTB) compared with symptom- free
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19 women.[15 17 18] Still, other studies have found no association between this
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21 phenomenon.[6 19] However, Czeizel and Puho have suggested that women with
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23 NVP had a lower risk of PTB.[20] A Norway prospective cohort study involving
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25 51,675 pregnant women found nausea to decrease the risk for PTB by 14% but did not
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27 find NVP associated with PTB.[9]
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34 To our knowledge, there has been only one case-control study, which was
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36 conducted in Chinese pregnant women that addressed the relationship between PTB
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38 and a severe form of NVP called *Hyperemesis Gravidarum*. [19] Information about the
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40 association between vomiting in the first trimester and risk of PTB in China is unclear.
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42 Furthermore, there has not been a study in which the population was grouped
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44 according to pre-pregnancy BMI to determine its contribution to the identification of
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46 the association between NVP and risk of PTB. Thus, our objective in the present study
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48 is to explore the association between vomiting in the first trimester and PTB as well
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50 as assess whether pre-pregnancy BMI modifies this association using a birth cohort
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52 study in Wuhan, China.
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Materials and methods

Study population

A retrospective cohort study was conducted in Wuhan China, utilizing data from the Wuhan Maternal and Child Health Management Information System (WMCHMIS). The WMCHMIS was introduced in our previous study.[21] Enrolled women included every pregnant woman who had a live, singleton newborn from January 1, 2010, to May 23, 2016. The study has been approved by the Wuhan Medical and Healthcare Center for Women and Children.

A total of 416,258 women were initially enrolled. We then excluded records with missing data on vomiting (n=95,886), offspring sex (n=22), maternal education (n=1,852), parity (n=972), and gravidity (n=48). Moreover, we also excluded those with a maternal age less than 15 (n=8) and more than 50 (n=7). The final study population consisted of 317,463 pregnancies or 76.27% of the initial population.

Variables

Vomiting in the first trimester was assessed when pregnant women first visited the women and children healthcare centers. Maternal age, education, parity, gravidity, pre-pregnancy weight, and height were self-reported at their first antenatal care visit while offspring sex and other obstetric information were provided by obstetric nurses documented in WMCHMIS. Information was audited by clinicians and obstetric nurses, and a warning would be activated when illogical data were input into WMCHMIS.

Vomiting was dichotomized into yes and no response formats. Maternal age was

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3 categorized into 3 groups: younger than 25, 25~34 years old, and 35 years old and
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5 older. A proxy for socioeconomic status was the maternal education which was
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7 categorized into 3 groups: less than high school, high school, and college. By parity,
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9 women were dichotomized into nullipara and multipara. Regarding gravidity, it was
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11 divided into less than 3 times and 3 times and more. Pre-pregnancy BMI was
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13 calculated as $\text{weight}/\text{height}^2$ and grouped into 4 categories according to Chinese
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15 standard of weight for adults.[22]
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21 The main outcome variable was PTB. PTB was defined as gestational age <37
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23 gestational weeks.[23] Gestational age was calculated using reports from mothers
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25 based on the first day of their last menstrual period. An ultrasound was routinely used
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27 to determine gestational age before 12 gestational weeks.
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30 31 *Statistical analysis*

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33 Results were presented as frequencies (%). A logistic regression model was used to
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35 estimate the association between vomiting in the first trimester and PTB. Results were
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37 adjusted for confounders including maternal age, education, parity, gravidity, and
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39 offspring sex in accord with previous studies.[9 24] We also employed a stratified
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41 analysis by pre-pregnancy BMI. Crude and adjusted relative risk (RR) statistics, as
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43 well as a 95% confidence interval (CI) were calculated. All statistical analyses were
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45 performed using SAS version 9.2 (SAS Statistical Institute, Inc., Cary, NC).
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50 51 **Results**

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53 In 317,463 pregnancies included in our study (Figure 1), gestational age ranged from
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55 28 weeks to 43 weeks. Altogether, 94,857 out of 317,463 pregnant women (29.88%)
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reported vomiting in the first trimester. And 5.00% (15,889) of the births were delivered preterm. Maternal demographics and characteristics are shown in Table 1. Women who were older than 35 years old, had a college education, were multipara, had more than 3 times gravidity, or had a higher pre-pregnancy BMI were more likely to have a PTB. PTB was observed to be more common in female babies than in male offspring.

Table1. Characteristics of women and infants

	Preterm (n=15,889, 5.00%)		Full-term (n=301,574, 95.00%)		P
	n	%	n	%	
Age at delivery					
<25	3091	3.62	82224	96.38	
25~34	11055	5.17	202692	94.83	<0.001
≥35	1743	9.47	16658	90.53	
Education level					
Less than high school	3519	4.55	73737	95.45	
High school	5010	4.71	101458	95.29	<0.001
College	7360	5.50	126379	94.50	
Offspring sex					
Female	9188	5.41	160671	94.59	
Male	6701	4.54	140903	95.46	<0.001
Parity					
Nullipara	11948	4.65	245121	95.35	
Multipara	3941	9.53	56453	93.47	<0.001
Gravidity					
<3	11471	4.59	238259	95.41	
≥3	4418	6.52	63315	93.48	<0.001
Pre-pregnancy BMI(kg/m²)					
Underweight (<18.5)	3118	4.21	70916	95.79	
Normal (18.5~23.9)	11083	5.03	209246	94.97	
Overweight(24~27.9)	1360	6.94	18226	93.06	<0.001
Obese(≥28)	328	9.33	3186	90.67	
Vomiting					

Yse	4978	5.25	89879	94.75	<0.001
No	10911	4.90	211695	95.10	

When vomiting women were compared with non-vomiting women, we found that vomiting in the first trimester produced a significant increase in risk for PTB, with RR=1.08 and 95% CI=1.04~1.13. The relationship still persisted (RR=1.05, 95% CI=1.02~1.09, Table 2) after adjustment for aforementioned confounders. In the additional stratified analyses, the results showed that vomiting in the first trimester was associated with PTB in underweight women (RR=1.08, 95%CI=1.04~1.17) and in women with a normal pre-pregnancy BMI (RR=1.06, 95%CI=1.02~1.11), but not among overweight and obese groups. After adjusting for the same set of confounders, no changes occurred in the results (Table 2).

Table 2 Association between vomiting and PTB and its association stratified by pre-pregnancy BMI

	Pre-term n (%)	Full-term n (%)	Unadjusted RR (95% CI)	<i>P</i>	Adjusted RR (95% CI)*	<i>P</i>
Vomiting						
Yes	4978(5.25)	89879(94.75)	1.075(1.038, 1.112)	<0.001	1.051(1.015, 1.088)	0.0048^a
No	10911(4.90)	211695(95.10)	1.00		1.00	
Underweight						
Vomiting						
Yes	810(4.49)	17216(95.56)	1.077(1.052,1.169)	0.0042	1.080(1.041,1.173)	0.0082^b
No	2308(4.12)	53700(95.86)	1.00		1.00	
Normal						
Vomiting						
Yes	3610(5.22)	65485(94.78)	1.061(1.041,1.105)	0.0048	1.059(1.017,1.0103)	0.0058^b
No	7473(4.94)	143761(95.06)	1.00		1.00	
Overweight						
Vomiting						
Yes	462(7.04)	6099(92.96)	1.023(0.911,1.149)	0.7012	1.011(0.899,1.136)	0.8547 ^b
No	898(6.89)	12127(93.11)	1.00		1.00	

Obese**Vomiting**

Yes	106(8.95)	1079(91.05)	0.932(0.731,1.189)	0.5719	0.928(0.727,1.185)	0.5508 ^b
No	222(9.53)	2107(90.47)	1.00		1.00	

RR: relative risk; CI: confidence interval.

^a Adjusted for maternal age, education, parity, gravidity, pre-pregnancy BMI, and offspring sex;

^b Adjusted for maternal age, education, parity, gravidity, and offspring sex.

Discussion

Nausea and vomiting (NVP) while pregnant has far reaching effects on the mental and physical health of mothers and their offspring. Little research has accrued on the association between NVP and PTB in China, especially taking into account pre-pregnancy BMI. This study showed that nearly 30% of Chinese pregnant women had experienced vomiting in the first trimester. The rate of vomiting in Chinese women was somewhat different than in other studies.[9 11 25-27] A Norwegian cohort study reported that the rate of NVP was 33% among 51,675 women with 15 gestational weeks,[9] which was higher than our findings. A previous meta-analysis estimated the rate of NVP in the USA was 68.6% including 23 studies composed of 67,602 women.[11] Conflicting results can likely be explained by heterogeneity of populations, methods, definitions and confounders.

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.[28 29] 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.[29] Women aged >35 had

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4 longer exposure times to chronic pathologies and unhealthy lifestyles,[30] and higher
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6 prevalence of maternal obesity in older mothers, which were associated with risks
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8 factors for PTB.[31] Several studies demonstrated that the lower the socio-economic
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10 and education level, the higher the probability of developing infection, and that was
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12 clearly associated with PTB before 30 weeks of gestation.[32 33]
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16 In this large cohort study conducted among Chinese women, we have found an
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18 association between vomiting in the first trimester and PTB before 37 weeks of
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20 gestation. When compared with non-vomiting pregnant women, women that
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22 experienced vomiting were at an increased risk of PTB. Our results were inconsistent
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24 with that of other studies.[15 18 34 35] For example, Andrew and Puho indicated that
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26 there was a significant association of vomiting with a decreased risk of PTB,[20] and
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28 Naumann et al. found that vomiting was not associated with PTB.[27] The differences
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30 found among these studies may be attributed to race, definition or classification of
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32 vomiting, and the differential sample sizes of the populations mentioned above.
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39 The possible causal link between vomiting and PTB remains elusive. The most
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41 common hypothesis proffered to explain the harmful effects of vomiting is based on
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43 the fact that vomiting leads to abnormal digestive function, which results in a lower
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45 nutrient intake of pregnant women.[14 36] Vomiting may also affect maternal and
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47 fetal physiology through dehydration and the modulation of stress-related risk
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49 factors.[37 38] Moreover, vomiting may cause low maternal weight gain during
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51 pregnancy, which has been associated with PTB as reported by Canadian research.[6]
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56 Additionally, our results reveal that vomiting was a risk factor for PTB in women
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4 with underweight and normal pre-pregnancy BMI, but not in overweight and obese
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6 women. Previous studies have estimated the risk factors for vomiting and PTB
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8 separately and found different effects of pre-pregnancy BMI on vomiting and
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10 PTB.[39-41] No study has assessed the association between vomiting and PTB by
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12 pre-pregnancy BMI. The biological mechanisms underlying the associations with
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14 maternal pre-pregnancy BMIs remain unclear. Gary et al. indicated that the
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16 relationship between pre-pregnancy BMI and risk of PTB were complex.[23]
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18 Although it was not statistically significant, a trend towards lower risk for PTB in
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20 obese women with vomiting was observed. We speculate that vomiting may have
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22 relatively few impacts on the nutrition of obese women due to their increased
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24 capacity for energy storage.
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31 Strengths of this study are as follows. First, this is the first study exploring the
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33 relationship between vomiting in the first trimester and PTB in Chinese women while
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35 assessing the association between PTB and vomiting by pre-pregnancy BMI status.
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37 Second, the data were collected from the large population-based cohort and linked to
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39 the WMCHMIS, providing thorough and detailed access to pregnancy and birth
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41 outcomes. Third, with such a large cohort size, many significant associations tend to
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43 appear, and the merit of these in the clinical setting is notable. However, there are two
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45 limitations. One is the reliance on self-reported data on vomiting. Retrospective
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47 evaluation of vomiting symptoms has been reported as a possible source of bias.[42]
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49 The other is that the prevalence of overweight and obesity were relatively low in our
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51 sample (6.17% and 1.10%, respectively) and the relationship between vomiting and
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4 PTB in women with a high pre-pregnancy BMI needs to be further assessed.
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6 7 **Conclusion**

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9 This study showed that vomiting presented an increased risk for PTB based on a large
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11 cohort study in China, although the effect was small. Vomiting was a risk for PTB in
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13 women who were underweight and normal weight based on their pre-pregnancy BMI.
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15 Although no significant association between vomiting and PTB in overweight and
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17 obese women was observed, clinicians should give all women suitable guidance for
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19 dealing with vomiting to ensure improved pregnancy outcomes. Finally, we recognize
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21 the need for greater clarity with respect to the association between vomiting and PTB
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23 and encourage researchers to build on our findings.
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28 29 **Acknowledgement**

30
31 We are extremely grateful to all the families who took part in this study, the staff of
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33 the Wuhan Health Bureau, and all the hospitals and community health centers
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35 involved in this study.
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38 39 **Ethics approval**

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41 The Institutional Review Board of Wuhan Medical and Healthcare Center for Women
42
43 and Children received and approved this study (approved on 10/13/2016).
44
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46 47 **Funding**

48
49 None.
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51 52 **Patient consent**

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54 Obtained.
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56 57 **Competing interests**

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4 None declared.

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6 **Data sharing statement**

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8 No additional data are available.

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11 **Contribution to authorship**

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13 RHH, YWC, BZ designed the research; YWC, YMZ, MZL analyzed data; RHH,
14
15 YWC, YL drafted the manuscript; ZMQ, MG, SQX, TZZ, BZ revised the
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19 manuscript.

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23 **References**

- 24
25
26 1. Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. The
27
28 Quarterly review of biology 2000;**75**(2):113-48
- 29
30
31 2. Koren G, Madjunkova S, Maltepe C. The protective effects of nausea and vomiting of pregnancy
32
33 against adverse fetal outcome--a systematic review. Reproductive toxicology 2014;**47**:77-80
34
35 doi: 10.1016/j.reprotox.2014.05.012[published Online First: Epub Date].
- 36
37
38 3. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during
39
40 pregnancy. The British journal of general practice : the journal of the Royal College of
41
42 General Practitioners 1993;**43**(371):245-8
- 43
44
45 4. Mazzotta P, Maltepe C, Navioz Y, Magee LA, Koren G. Attitudes, management and consequences of
46
47
48 nausea and vomiting of pregnancy in the United States and Canada. International journal of
49
50 gynaecology and obstetrics: the official organ of the International Federation of Gynaecology
51
52 and Obstetrics 2000;**70**(3):359-65
- 53
54
55
56 5. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a
57
58
59
60

- burden of early pregnancy. *The Australian & New Zealand journal of obstetrics & gynaecology* 2000;**40**(4):397-401
6. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstetrics and gynecology* 2006;**107**(2 Pt 1):285-92 doi: 10.1097/01.AOG.0000195060.22832.cd[published Online First: Epub Date].
7. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique* 2013;**20**(2):e171-83
8. Koch KL, Frissora CL. Nausea and vomiting during pregnancy. *Gastroenterology clinics of North America* 2003;**32**(1):201-34, vi
9. Chortatos A, Haugen M, Iversen PO, et al. Pregnancy complications and birth outcomes among women experiencing nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study. *BMC Pregnancy Childbirth* 2015;**15**:138 doi: 10.1186/s12884-015-0580-6[published Online First: Epub Date].
10. Kallen B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta obstetricia et gynecologica Scandinavica* 2003;**82**(10):916-20
11. Einarson TR, Piwko C, Koren G. Prevalence of nausea and vomiting of pregnancy in the USA: a meta analysis. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique* 2013;**20**(2):e163-70
12. Chin RK. Antenatal complications and perinatal outcome in patients with nausea and vomiting-complicated pregnancy. *European journal of obstetrics, gynecology, and reproductive biology* 1989;**33**(3):215-9

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42
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47
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53
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59
60
13. Chan OK, Sahota DS, Leung TY, Chan LW, Fung TY, Lau TK. Nausea and vomiting in health-related quality of life among Chinese pregnant women. *The Australian & New Zealand journal of obstetrics & gynaecology* 2010;**50**(6):512-8 doi: 10.1111/j.1479-828X.2010.01216.x[published Online First: Epub Date]].
14. Birkeland E, Stokke G, Tangvik RJ, et al. Norwegian PUQE (Pregnancy-Unique Quantification of Emesis and nausea) identifies patients with hyperemesis gravidarum and poor nutritional intake: a prospective cohort validation study. *PLoS one* 2015;**10**(4):e0119962 doi: 10.1371/journal.pone.0119962[published Online First: Epub Date]].
15. Roseboom TJ, Ravelli AC, van der Post JA, Painter RC. Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum. *European journal of obstetrics, gynecology, and reproductive biology* 2011;**156**(1):56-9 doi: 10.1016/j.ejogrb.2011.01.010[published Online First: Epub Date]].
16. Chan RL, Olshan AF, Savitz DA, et al. Severity and duration of nausea and vomiting symptoms in pregnancy and spontaneous abortion. *Human reproduction* 2010;**25**(11):2907-12 doi: 10.1093/humrep/deq260[published Online First: Epub Date]].
17. Paauw JD, Bierling S, Cook CR, Davis AT. Hyperemesis gravidarum and fetal outcome. *JPEN. Journal of parenteral and enteral nutrition* 2005;**29**(2):93-6
18. Temming L, Franco A, Istwan N, et al. Adverse pregnancy outcomes in women with nausea and vomiting of pregnancy. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet* 2014;**27**(1):84-8 doi: 10.3109/14767058.2013.806473[published Online First: Epub Date]].

- 1
2
3
4 19. Zhang J, Cai WW. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes.
5
6 Epidemiology 1991;**2**(6):454-7
7
8
9 20. Czeizel AE, Puho E. Association between severe nausea and vomiting in pregnancy and lower rate
10
11 of preterm births. Paediatric and perinatal epidemiology 2004;**18**(4):253-9 doi:
12
13 10.1111/j.1365-3016.2004.00568.x[published Online First: Epub Date]].
14
15
16 21. Zhou A, Xiong C, Hu R, et al. Pre-Pregnancy BMI, Gestational Weight Gain, and the Risk of
17
18 Hypertensive Disorders of Pregnancy: A Cohort Study in Wuhan, China. PloS one
19
20
21 2015;**10**(8):e0136291 doi: 10.1371/journal.pone.0136291[published Online First: Epub Date]].
22
23
24 22. Wang Y, Mi J, Shan XY, Wang QJ, Ge KY. Is China facing an obesity epidemic and the
25
26 consequences? The trends in obesity and chronic disease in China. International journal of
27
28 obesity (2005) 2007;**31**(1):177-88 doi: 10.1038/sj.ijo.0803354[published Online First: Epub
29
30 Date]].
31
32
33 23. Shaw GM, Wise PH, Mayo J, et al. Maternal prepregnancy body mass index and risk of
34
35 spontaneous preterm birth. Paediatric and perinatal epidemiology 2014;**28**(4):302-11 doi:
36
37 10.1111/ppe.12125[published Online First: Epub Date]].
38
39
40 24. Vikanes AV, Stoer NC, Magnus P, Grjibovski AM. Hyperemesis gravidarum and pregnancy
41
42 outcomes in the Norwegian Mother and Child Cohort - a cohort study. BMC pregnancy and
43
44 childbirth 2013;**13**:169 doi: 10.1186/1471-2393-13-169[published Online First: Epub Date]].
45
46
47 25. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy.
48
49
50
51
52
53
54
55 26. Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with
56
57 pregnancy outcome. American journal of obstetrics and gynecology 1986;**155**(5):1017-22
58
59
60

- 1
2
3
4 27. Naumann CR, Zelig C, Napolitano PG, Ko CW. Nausea, vomiting, and heartburn in pregnancy: a
5
6 prospective look at risk, treatment, and outcome. *The journal of maternal-fetal & neonatal*
7
8 *medicine : the official journal of the European Association of Perinatal Medicine, the*
9
10 *Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal*
11
12 *Obstet* 2012;**25**(8):1488-93 doi: 10.3109/14767058.2011.644363[published Online First: Epub
13
14 Date]].
- 15
16
17
18 28. Laopaiboon M, Lumbiganon P, Intarut N, et al. Advanced maternal age and pregnancy outcomes: a
19
20 multicountry assessment. *BJOG : an international journal of obstetrics and gynaecology*
21
22 2014;**121 Suppl 1**:49-56 doi: 10.1111/1471-0528.12659[published Online First: Epub Date]].
- 23
24
25
26 29. Araya BM, Diaz M, Paredes D, Ortiz J. Association between preterm birth and its subtypes and
27
28 maternal sociodemographic characteristics during the post-transitional phase in a developing
29
30 country with a very high human development index. *Public health* 2017;**147**:39-46 doi:
31
32 10.1016/j.puhe.2017.01.027[published Online First: Epub Date]].
- 33
34
35
36 30. Chen X, Scholl TO. Association of elevated free fatty acids during late pregnancy with preterm
37
38 delivery. *Obstetrics and gynecology* 2008;**112**(2 Pt 1):297-303 doi:
39
40 10.1097/AOG.0b013e3181802150[published Online First: Epub Date]].
- 41
42
43
44 31. Passini R, Jr., Cecatti JG, Lajos GJ, et al. Brazilian multicentre study on preterm birth (EMIP):
45
46 prevalence and factors associated with spontaneous preterm birth. *PloS one*
47
48 2014;**9**(10):e109069 doi: 10.1371/journal.pone.0109069[published Online First: Epub Date]].
- 49
50
51
52 32. Ovalle A, Kakarieka E, Rencoret G, et al. [Risk factors for preterm deliveries in a public hospital].
53
54 *Revista medica de Chile* 2012;**140**(1):19-29 doi: /S0034-98872012000100003[published
55
56 Online First: Epub Date]].
- 57
58
59
60

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2
3
4 33. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth.
5
6 Lancet 2008;**371**(9606):75-84 doi: 10.1016/S0140-6736(08)60074-4[published Online First:
7
8 Epub Date]].
9
- 10
11 34. Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of
12
13 hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG : an
14
15 international journal of obstetrics and gynaecology 2011;**118**(11):1302-13 doi:
16
17 10.1111/j.1471-0528.2011.03023.x[published Online First: Epub Date]].
18
19
- 20
21 35. Schiff MA, Reed SD, Daling JR. The sex ratio of pregnancies complicated by hospitalisation for
22
23 hyperemesis gravidarum. BJOG : an international journal of obstetrics and gynaecology
24
25 2004;**111**(1):27-30
26
27
- 28
29 36. Lee J-I, Lee J-A, Lim H-S. Morning sickness reduces dietary diversity, nutrient intakes, and infant
30
31 outcome of pregnant women. Nutrition Research 2004;**24**(7):531-40 doi:
32
33 10.1016/j.nutres.2003.10.011[published Online First: Epub Date]].
34
35
- 36
37 37. Jarnfelt-Samsioe A, Eriksson B, Waldenstrom J, Samsioe G. Some new aspects on emesis
38
39 gravidarum. Relations to clinical data, serum electrolytes, total protein and creatinine.
40
41 Gynecologic and obstetric investigation 1985;**19**(4):174-86
42
43
- 44
45 38. Haugen M, Vikanes A, Brantsaeter AL, Meltzer HM, Grjibovski AM, Magnus P. Diet before
46
47 pregnancy and the risk of hyperemesis gravidarum. The British journal of nutrition
48
49 2011;**106**(4):596-602 doi: 10.1017/s0007114511000675[published Online First: Epub Date]].
50
51
- 52
53 39. Huxley RR. Nausea and vomiting in early pregnancy: its role in placental development. Obstetrics
54
55 and gynecology 2000;**95**(5):779-82
56
57
- 58
59 40. Girsen AI, Mayo JA, Carmichael SL, et al. Women's prepregnancy underweight as a risk factor for
60

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2
3
4 preterm birth: a retrospective study. BJOG : an international journal of obstetrics and
5
6 gynaecology 2016;**123**(12):2001-07 doi: 10.1111/1471-0528.14027[published Online First:
7
8 Epub Date]].
9

10
11 41. Pan Y, Zhang S, Wang Q, et al. Investigating the association between prepregnancy body mass
12
13 index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant
14
15 women in rural China. BMJ open 2016;**6**(6):e011227 doi:
16
17 10.1136/bmjopen-2016-011227[published Online First: Epub Date]].
18
19

20
21 42. Koren G, Maltepe C, Navioz Y, Wolpin J. Recall bias of the symptoms of nausea and vomiting of
22
23 pregnancy. American journal of obstetrics and gynecology 2004;**190**(2):485-8 doi:
24
25 10.1016/j.ajog.2003.08.039[published Online First: Epub Date].
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Figure legends

Figure 1. Flow chart of population selection

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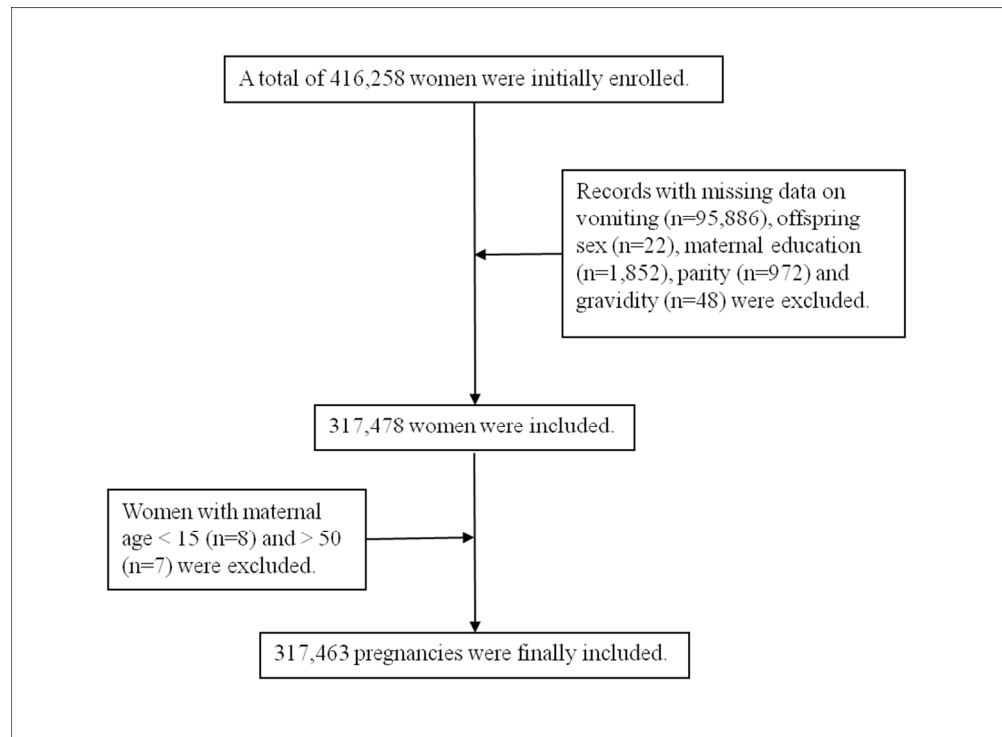


Figure 1 Flow chart of population selection

186x136mm (150 x 150 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	No. of Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	NR
		(e) Describe any sensitivity analyses	NR
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8-9

		which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Association between vomiting in the first trimester and preterm birth: a retrospective birth cohort study in Wuhan, China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017309.R2
Article Type:	Research
Date Submitted by the Author:	02-Aug-2017
Complete List of Authors:	<p>Hu, Ronghua; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Chen, Yawen; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Zhang, Yiming; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Qian, Zhengmin ; Saint Louis University, Department of Epidemiology, School of Public Health</p> <p>Liu, Yan; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Vaughn, MG; Saint Louis University, School of Social Work</p> <p>Xu, Shunqing; Tongji Medical College, Huazhong University of Science and Technology, Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health, School of Public Health</p> <p>Zheng, Tongzhang; Brown University, Department of Epidemiology, School of Public Health</p> <p>Liu, Mingzhu; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Zhang, Bin; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p>
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	PRETERM BIRTH, Cohort study, pre-pregnancy body mass index, vomiting

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**Association between vomiting in the first trimester and preterm birth:
a retrospective birth cohort study in Wuhan, China**

Ronghua Hu^{1§}, Yawen Chen^{1§}, Yiming Zhang¹, Zhengmin Qian², Yan Liu¹, Michael
G. Vaughn², Shunqing Xu³, Tongzhang Zheng⁴, Mingzhu Liu¹, Bin Zhang^{1*}

¹ Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, Hubei,
People's Republic of China

² Department of Epidemiology, College for Public Health and Social Justice, Saint
Louis University, MO, United States of America

³ Key Laboratory of Environment and Health, School of Public Health, Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, Hubei,
People's Republic of China

⁴ Department of Epidemiology, School of Public Health, Providence, Brown
University, RI, United States of America

[§]These authors contributed equally to this work

***Corresponding author**

Full name: Bin Zhang

Postal address: No.100 Hongkong Road, Wuhan 430014, Hubei, China,

E-mail: mchwhzb@163.com

Telephone and fax number: +86-027-82433149

Abstract

Objective: Although vomiting in the first trimester has been reported to be associated with preterm birth (PTB), findings supporting this association remain inconsistent. Our aim was to assess the association between vomiting and PTB, as well as evaluate if the association is modified by pre-pregnancy body mass index (BMI).

Design: A retrospective cohort study.

Setting: Wuhan, a central city of China.

Participants: A total of 317,463 pregnant women who had a live, singleton newborn from January 1, 2010, to May 23, 2016 were enrolled in our study.

Main outcome measure: PTB was defined as gestational age <37 gestational weeks. Gestational age was calculated using reports from mothers based on the first day of their last menstrual period. An ultrasound was routinely used to determine gestational age before 12 gestational weeks.

Results: Of the 317,463 pregnant women, 29.88% (94,857) experienced vomiting in the first trimester and 5.00% (15,889) experienced a PTB. Vomiting in the first trimester increased the risk for PTB and the multivariable adjusted odds ratio (OR) was 1.05 (95% confidence interval (CI) = 1.02~1.09). In the stratified analyses, the association of vomiting in the first trimester was significant among underweight women (adjusted OR=1.08, 95%CI=1.04~1.17) and normal pre-pregnancy BMI women (adjusted OR=1.06, 95%CI=1.02~1.11), but not in overweight women (adjusted OR=1.01, 95% CI=0.90~1.14) and obese women (adjusted OR=0.93, 95% CI=0.73~1.19).

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4 **Conclusions:** Our study indicates that vomiting in the first trimester was associated
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6 with PTB. Additionally, women with underweight and normal pre-pregnancy BMI
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8 that experienced vomiting are more likely to have a PTB.
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11 **Keywords:** vomiting; preterm birth; pre-pregnancy body mass index
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14 15 16 **Strengths and limitations of this study** 17

- 18 1. The present study is a cohort study enrolled a large population of 317,463 pregnant
19 women.
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21
- 22 2. This is the first study exploring the relationship between vomiting in the first
23 trimester and PTB in Chinese women by pre-pregnancy BMI status.
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25
- 26 3. Vomiting symptoms was based on self-reported, which may be a possible source of
27 bias.
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- 30 4. The prevalence of overweight and obesity were relatively low in our sample, and
31 the relationship between vomiting and PTB in women with a high pre-pregnancy BMI
32 needs to be further assessed.
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Introduction

Nausea and vomiting in pregnancy (NVP) is a collection of symptoms composed of nausea alone, or nausea in combination with vomiting.[1] This condition typically starts prior to 9 weeks of gestation and subsides by the end of the first trimester; however, this condition has been shown to continue into the second trimester in up to 25% of pregnant women and for 0.3-2.3% into the third trimester.[2] NVP has an important effect on both individuals and society as it causes emotional distress, depression, and can have a negative effect on a woman's activities and relationships.[3 4] NVP also has been found to lead to loss of time at work and a decrease in job productivity.[5] The etiology of NVP remains unknown, although it is currently believed to be related to early pregnancy hormones.[6]

Almost 70% of women worldwide experience NVP.[7] The average rate of vomiting only in early pregnancy is 47.1%, and the reported rates generally range from 22.3% to 63.5%.[8] A Norwegian cohort investigation reported that the rate of NVP was 33% among 51,675 women.[9] Källén et al. studied the occurrence of NVP via questionnaires in 3,675 Swedish pregnant women and observed that 38.3% of pregnant women reported vomiting in early pregnancy.[10] One previous meta-analysis, which included 23 studies comprised of 67,602 women,[11] estimated the rate of NVP in the USA to be as high as 68.6%. Meanwhile, studies on the rate of NVP in China are few and are limited by their small sample sizes. Chin et al.[12] conducted a study in a district hospital in Hong Kong in 1989 and found that the incidence of NVP was 74.9% among 1,453 patients. Another cross-sectional study

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4 conducted in a University obstetric unit in Hong Kong revealed that the prevalence of
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6 NVP was 90.9% among 396 women.[13]
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9 In previous studies, NVP was not found to be associated with primary maternal
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11 diseases such as gastrointestinal infections or allergies.[8] Recently there was a
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13 resurgence of interest in topics related to NVP, such as death,[14] pregnancy
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15 complications,[15] and birth outcomes.[16] Some studies reported that women with
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17 NVP were more likely to have a preterm birth (PTB) compared with symptom- free
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19 women.[15 17 18] Still, other studies have found no association between this
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21 phenomenon.[6 19] However, Czeizel and Puho have suggested that women with
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23 NVP had a lower risk of PTB.[20] A Norway prospective cohort study involving
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25 51,675 pregnant women found nausea to decrease the risk for PTB by 14% but did not
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27 find NVP associated with PTB.[9]
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34 To our knowledge, there has been only one case-control study, which was
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36 conducted in Chinese pregnant women that addressed the relationship between PTB
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38 and a severe form of NVP called *Hyperemesis Gravidarum*. [19] Information about the
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40 association between vomiting in the first trimester and risk of PTB in China is unclear.
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42 Furthermore, there has not been a study in which the population was grouped
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44 according to pre-pregnancy BMI to determine its contribution to the identification of
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46 the association between NVP and risk of PTB. Thus, our objective in the present study
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48 is to explore the association between vomiting in the first trimester and PTB as well
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50 as assess whether pre-pregnancy BMI modifies this association using a birth cohort
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52 study in Wuhan, China.
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Materials and methods

Study population

A retrospective cohort study was conducted in Wuhan China, utilizing data from the Wuhan Maternal and Child Health Management Information System (WMCHMIS). The WMCHMIS was introduced in our previous study.[21] Enrolled women included every pregnant woman who had a live, singleton newborn from January 1, 2010, to May 23, 2016. The study has been approved by the Wuhan Medical and Healthcare Center for Women and Children.

A total of 416,258 women were initially enrolled. We then excluded records with missing data on vomiting (n=95,886), offspring sex (n=22), maternal education (n=1,852), parity (n=972), and gravidity (n=48). Moreover, we also excluded those with a maternal age less than 15 (n=8) and more than 50 (n=7). The final study population consisted of 317,463 pregnancies or 76.27% of the initial population.

Variables

Vomiting in the first trimester was assessed when pregnant women first visited the women and children healthcare centers. Maternal age, education, parity, gravidity, pre-pregnancy weight, and height were self-reported at their first antenatal care visit while offspring sex and other obstetric information were provided by midwives documented in WMCHMIS. Information was audited by clinicians and obstetric nurses, and a warning would be activated when illogical data were input into WMCHMIS.

Vomiting was dichotomized into yes and no response formats. Maternal age was

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4 categorized into 3 groups: younger than 25, 25~34 years old, and 35 years old and
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6 older. A proxy for socioeconomic status was the maternal education which was
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8 categorized into 3 groups: less than high school, high school, and college. By parity,
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10 women were dichotomized into nullipara and multipara. Regarding gravidity, it was
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12 divided into less than 3 times and 3 times and more. Pre-pregnancy BMI was
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14 calculated as $\text{weight}/\text{height}^2$ and grouped into 4 categories according to Chinese
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16 standard of weight for adults.[22]
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21 The main outcome variable was PTB. PTB was defined as gestational age <37
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23 gestational weeks.[23] Gestational age was calculated using reports from mothers
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25 based on the first day of their last menstrual period. An ultrasound was routinely used
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27 to determine gestational age before 12 gestational weeks.
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30 31 *Statistical analysis*

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33 Results were presented as frequencies (%). Difference between PTB group and
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35 full-term group were assessed by Chi-square tests. A logistic regression model was
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37 used to estimate the association between vomiting in the first trimester and PTB.
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39 Results were adjusted for confounders including maternal age, education, parity,
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41 gravidity, pre-pregnancy BMI, and offspring sex in accord with previous studies.[9 24]
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43 We also employed a stratified analysis by pre-pregnancy BMI and the confounders
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45 adjusted in stratified analysis were maternal age, education, parity, gravidity, and
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47 offspring sex. Crude and adjusted odds ratios (ORs) statistics, as well as a 95%
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49 confidence interval (CI) were calculated. All statistical analyses were performed using
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Results

In 317,463 pregnancies included in our study (Figure 1), gestational age ranged from 28 weeks to 43 weeks. Altogether, 94,857 out of 317,463 pregnant women (29.88%) reported vomiting in the first trimester. And 5.00% (15,889) of the births were delivered preterm. Maternal demographics and characteristics are shown in Table 1. Women who were older than 35 years old, had a college education, were multipara, had more than 3 times gravidity, or had a higher pre-pregnancy BMI were more likely to have a PTB. PTB was observed to be more common in female babies than in male offspring.

Table 1. Characteristics of women and infants

	Preterm (n=15,889, 5.00%)		Full-term (n=301,574, 95.00%)		P
	n	%	n	%	
Age at delivery					
<25	3091	3.62	82224	96.38	
25~34	11055	5.17	202692	94.83	<0.001
≥35	1743	9.47	16658	90.53	
Education level					
Less than high school	3519	4.55	73737	95.45	
High school	5010	4.71	101458	95.29	<0.001
College	7360	5.50	126379	94.50	
Offspring sex					
Male	9188	5.41	160671	94.59	
Female	6701	4.54	140903	95.46	<0.001
Parity					
Nullipara	11948	4.65	245121	95.35	
Multipara	3941	6.53	56453	93.47	<0.001
Gravidity					
<3	11471	4.59	238259	95.41	
≥3	4418	6.52	63315	93.48	<0.001
Pre-pregnancy BMI(kg/m²)					

Underweight (<18.5)	3118	4.21	70916	95.79	
Normal (18.5~23.9)	11083	5.03	209246	94.97	<0.001
Overweight(24~27.9)	1360	6.94	18226	93.06	
Obese(\geq 28)	328	9.33	3186	90.67	
Vomiting					
Yse	4978	5.25	89879	94.75	<0.001
No	10911	4.90	211695	95.10	

When vomiting women were compared with non-vomiting women, we found that vomiting in the first trimester produced a significant increase in risk for PTB, with OR=1.08 and 95% CI=1.04~1.13. The relationship still persisted (OR=1.05, 95% CI=1.02~1.09, Table 2) after adjustment for aforementioned confounders. In the additional stratified analyses, the results showed that vomiting in the first trimester was associated with PTB in underweight women (OR=1.08, 95%CI=1.04~1.17) and in women with a normal pre-pregnancy BMI (OR=1.06, 95%CI=1.02~1.11), but not among overweight and obese groups. After adjusting for the same set of confounders, no changes occurred in the results (Table 2).

Table 2 Association between vomiting and PTB and its association stratified by pre-pregnancy BMI

	Pre-term n (%)	Full-term n (%)	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)*	<i>P</i>
Vomiting						
Yes	4978(5.25)	89879(94.75)	1.075(1.038, 1.112)	<0.001	1.051(1.015, 1.088)	0.0048^a
No	10911(4.90)	211695(95.10)	1.00		1.00	
Underweight						
Vomiting						
Yes	810(4.49)	17216(95.56)	1.077(1.052,1.169)	0.0042	1.080(1.041,1.173)	0.0082^b
No	2308(4.12)	53700(95.86)	1.00		1.00	
Normal						
Vomiting						
Yes	3610(5.22)	65485(94.78)	1.061(1.041,1.105)	0.0048	1.059(1.017,1.0103)	0.0058^b

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No	7473(4.94)	143761(95.06)	1.00		1.00	
Overweight						
Vomiting						
Yes	462(7.04)	6099(92.96)	1.023(0.911,1.149)	0.7012	1.011(0.899,1.136)	0.8547 ^b
No	898(6.89)	12127(93.11)	1.00		1.00	
Obese						
Vomiting						
Yes	106(8.95)	1079(91.05)	0.932(0.731,1.189)	0.5719	0.928(0.727,1.185)	0.5508 ^b
No	222(9.53)	2107(90.47)	1.00		1.00	

OR: odds ratio; CI: confidence interval.

^a Adjusted for maternal age, education, parity, gravidity, pre-pregnancy BMI, and offspring sex;

^b Adjusted for maternal age, education, parity, gravidity, and offspring sex.

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).

Discussion

Nausea and vomiting (NVP) while pregnant has far reaching effects on the mental and physical health of mothers and their offspring. Little research has accrued on the association between NVP and PTB in China, especially taking into account pre-pregnancy BMI. This study showed that nearly 30% of Chinese pregnant women had experienced vomiting in the first trimester. The rate of vomiting in Chinese women was somewhat different than in other studies.[9 11 25-27] A Norwegian cohort study reported that the rate of NVP was 33% among 51,675 women with 15 gestational weeks,[9] which was higher than our findings. A previous meta-analysis estimated the rate of NVP in the USA was 68.6% including 23 studies composed of 67,602 women.[11] Conflicting results can likely be explained by heterogeneity of

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4 populations, methods, definitions and confounders.

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6 Our results showed that socio-demographic factors, such as age, education level,
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8 parity, and gravidity, might influence PTB. Previous studies have indicated that
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10 women with advanced maternal age were associated with increased risk of PTB.[28
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12 29] Araya BM et al. reported that age >35 years, delivery of more than two fetuses,
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14 and <8 years of education were risks factors for PTB.[29] Women aged >35 had
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16 longer exposure times to chronic pathologies and unhealthy lifestyles,[30] and higher
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18 prevalence of maternal obesity in older mothers, which were associated with risks
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20 factors for PTB.[31] Several studies demonstrated that the lower the socio-economic
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22 and education level, the higher the probability of developing infection, and that was
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24 clearly associated with PTB before 30 weeks of gestation.[32 33]
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31 In this large cohort study conducted among Chinese women, we have found an
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33 association between vomiting in the first trimester and PTB before 37 weeks of
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35 gestation. When compared with non-vomiting pregnant women, women that
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37 experienced vomiting were at an increased risk of PTB. Our results were inconsistent
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39 with that of other studies.[15 18 34 35] For example, Andrew and Puho indicated that
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41 there was a significant association of vomiting with a decreased risk of PTB,[20] and
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43 Naumann et al. found that vomiting was not associated with PTB.[27] The differences
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45 found among these studies may be attributed to race, definition or classification of
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47 vomiting, and the differential sample sizes of the populations mentioned above.
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53 The possible causal link between vomiting and PTB remains elusive. The most
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55 common hypothesis proffered to explain the harmful effects of vomiting is based on
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4 the fact that vomiting leads to abnormal digestive function, which results in a lower
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6 nutrient intake of pregnant women.[14 36] Vomiting may also affect maternal and
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8 fetal physiology through dehydration and the modulation of stress-related risk
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10 factors.[37 38] Moreover, vomiting may cause low maternal weight gain during
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12 pregnancy, which has been associated with PTB as reported by Canadian research.[6]
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16 Additionally, our results reveal that vomiting was a risk factor for PTB in women
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18 with underweight and normal pre-pregnancy BMI, but not in overweight and obese
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20 women. Previous studies have estimated the risk factors for vomiting and PTB
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22 separately and found different effects of pre-pregnancy BMI on vomiting and
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24 PTB.[39-41] No study has assessed the association between vomiting and PTB by
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26 pre-pregnancy BMI. The biological mechanisms underlying the associations with
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28 maternal pre-pregnancy BMIs remain unclear. Gary et al. indicated that the
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30 relationship between pre-pregnancy BMI and risk of PTB were complex.[23]
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32 Although it was not statistically significant, a trend towards lower risk for PTB in
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34 obese women with vomiting was observed. We speculate that vomiting may have
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36 relatively few impacts on the nutrition of obese women due to their increased
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38 capacity for energy storage.
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47 Strengths of this study are as follows. First, this is the first study exploring the
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49 relationship between vomiting in the first trimester and PTB in Chinese women while
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51 assessing the association between PTB and vomiting by pre-pregnancy BMI status.
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53 Second, the data were collected from the large population-based cohort and linked to
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55 the WMCHMIS, providing thorough and detailed access to pregnancy and birth
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4 outcomes. Third, with such a large cohort size, many significant associations tend to
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6 appear, and the merit of these in the clinical setting is notable. However, there are two
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8 limitations. One is the reliance on self-reported data on vomiting. Retrospective
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10 evaluation of vomiting symptoms has been reported as a possible source of bias.[42]
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12 The other is that the prevalence of overweight and obesity were relatively low in our
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14 sample (6.17% and 1.10%, respectively) and the relationship between vomiting and
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16 PTB in women with a high pre-pregnancy BMI needs to be further assessed.
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20 21 **Conclusion**

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23 This study showed that vomiting presented an increased risk for PTB based on a large
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25 cohort study in China, although the effect was small. Vomiting was a risk for PTB in
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27 women who were underweight and normal weight based on their pre-pregnancy BMI.
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29 Although no significant association between vomiting and PTB in overweight and
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31 obese women was observed, clinicians should give all women suitable guidance for
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33 dealing with vomiting to ensure improved pregnancy outcomes. Finally, we recognize
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35 the need for greater clarity with respect to the association between vomiting and PTB
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37 and encourage researchers to build on our findings.
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43 44 **Acknowledgement**

45
46 We are extremely grateful to all the families who took part in this study, the staff of
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48 the Wuhan Health Bureau, and all the hospitals and community health centers
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50 involved in this study.
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53 54 **Ethics approval**

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56 The Institutional Review Board of Wuhan Medical and Healthcare Center for Women
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4 and Children received and approved this study (approved on 10/13/2016).
5

6 **Funding**

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8 None.
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10 **Patient consent**

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12 Obtained.
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14 **Competing interests**

15
16 None declared.
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18 **Data sharing statement**

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20 No additional data are available.
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22 **Contribution to authorship**

23
24 RHH, YWC, BZ designed the research; YWC, YMZ, MZL analyzed data; RHH,
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26 YWC, YL drafted the manuscript; ZMQ, MGW, SQX, TZZ, BZ revised the
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28 manuscript.
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39 **References**

- 40
41 1. Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. The
42
43 Quarterly review of biology 2000;**75**(2):113-48
44
45
46 2. Koren G, Madjunkova S, Maltepe C. The protective effects of nausea and vomiting of pregnancy
47
48 against adverse fetal outcome--a systematic review. Reproductive toxicology 2014;**47**:77-80
49
50 doi: 10.1016/j.reprotox.2014.05.012[published Online First: Epub Date].
51
52
53 3. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during
54
55 pregnancy. The British journal of general practice : the journal of the Royal College of
56
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45
46
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50
51
52
53
54
55
56
57
58
59
60
- General Practitioners 1993;**43**(371):245-8
4. Mazzotta P, Maltepe C, Navioz Y, Magee LA, Koren G. Attitudes, management and consequences of nausea and vomiting of pregnancy in the United States and Canada. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2000;**70**(3):359-65
5. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. *The Australian & New Zealand journal of obstetrics & gynaecology* 2000;**40**(4):397-401
6. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstetrics and gynecology* 2006;**107**(2 Pt 1):285-92 doi: 10.1097/01.AOG.0000195060.22832.cd[published Online First: Epub Date]].
7. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique* 2013;**20**(2):e171-83
8. Koch KL, Frissora CL. Nausea and vomiting during pregnancy. *Gastroenterology clinics of North America* 2003;**32**(1):201-34, vi
9. Chortatos A, Haugen M, Iversen PO, et al. Pregnancy complications and birth outcomes among women experiencing nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study. *BMC Pregnancy Childbirth* 2015;**15**:138 doi: 10.1186/s12884-015-0580-6[published Online First: Epub Date]].
10. Kallen B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta obstetricia et gynecologica Scandinavica* 2003;**82**(10):916-20

- 1
2
3
4 11. Einarson TR, Piwko C, Koren G. Prevalence of nausea and vomiting of pregnancy in the USA: a
5
6 meta analysis. *Journal of population therapeutics and clinical pharmacology = Journal de la*
7
8 *therapeutique des populations et de la pharmacologie clinique* 2013;**20**(2):e163-70
9
10
11 12. Chin RK. Antenatal complications and perinatal outcome in patients with nausea and
12
13 vomiting-complicated pregnancy. *European journal of obstetrics, gynecology, and*
14
15 *reproductive biology* 1989;**33**(3):215-9
16
17
18 13. Chan OK, Sahota DS, Leung TY, Chan LW, Fung TY, Lau TK. Nausea and vomiting in
19
20 health-related quality of life among Chinese pregnant women. *The Australian & New Zealand*
21
22 *journal of obstetrics & gynaecology* 2010;**50**(6):512-8 doi:
23
24 10.1111/j.1479-828X.2010.01216.x[published Online First: Epub Date]].
25
26
27 14. Birkeland E, Stokke G, Tangvik RJ, et al. Norwegian PUQE (Pregnancy-Unique Quantification of
28
29 Emesis and nausea) identifies patients with hyperemesis gravidarum and poor nutritional
30
31 intake: a prospective cohort validation study. *PloS one* 2015;**10**(4):e0119962 doi:
32
33 10.1371/journal.pone.0119962[published Online First: Epub Date]].
34
35
36 15. Roseboom TJ, Ravelli AC, van der Post JA, Painter RC. Maternal characteristics largely explain
37
38 poor pregnancy outcome after hyperemesis gravidarum. *European journal of obstetrics,*
39
40 *gynecology, and reproductive biology* 2011;**156**(1):56-9 doi:
41
42 10.1016/j.ejogrb.2011.01.010[published Online First: Epub Date]].
43
44
45 16. Chan RL, Olshan AF, Savitz DA, et al. Severity and duration of nausea and vomiting symptoms in
46
47 pregnancy and spontaneous abortion. *Human reproduction* 2010;**25**(11):2907-12 doi:
48
49 10.1093/humrep/deq260[published Online First: Epub Date]].
50
51
52 17. Paauw JD, Bierling S, Cook CR, Davis AT. Hyperemesis gravidarum and fetal outcome. *JPEN.*
53
54
55
56
57
58
59
60

- Journal of parenteral and enteral nutrition 2005;**29**(2):93-6
18. Temming L, Franco A, Istwan N, et al. Adverse pregnancy outcomes in women with nausea and vomiting of pregnancy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2014;**27**(1):84-8 doi: 10.3109/14767058.2013.806473[published Online First: Epub Date]].
19. Zhang J, Cai WW. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. Epidemiology 1991;**2**(6):454-7
20. Czeizel AE, Puho E. Association between severe nausea and vomiting in pregnancy and lower rate of preterm births. Paediatric and perinatal epidemiology 2004;**18**(4):253-9 doi: 10.1111/j.1365-3016.2004.00568.x[published Online First: Epub Date]].
21. Zhou A, Xiong C, Hu R, et al. Pre-Pregnancy BMI, Gestational Weight Gain, and the Risk of Hypertensive Disorders of Pregnancy: A Cohort Study in Wuhan, China. PloS one 2015;**10**(8):e0136291 doi: 10.1371/journal.pone.0136291[published Online First: Epub Date]].
22. Wang Y, Mi J, Shan XY, Wang QJ, Ge KY. 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]].
23. 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[published Online First: Epub Date]].
24. Vikanes AV, Stoer NC, Magnus P, Grjibovski AM. Hyperemesis gravidarum and pregnancy

- 1
2
3
4 outcomes in the Norwegian Mother and Child Cohort - a cohort study. BMC pregnancy and
5
6 childbirth 2013;**13**:169 doi: 10.1186/1471-2393-13-169[published Online First: Epub Date]].
7
8
9 25. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy.
10
11 Obstetrics and gynecology 1985;**66**(5):612-6
12
13 26. Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with
14
15 pregnancy outcome. American journal of obstetrics and gynecology 1986;**155**(5):1017-22
16
17
18 27. Naumann CR, Zelig C, Napolitano PG, Ko CW. Nausea, vomiting, and heartburn in pregnancy: a
19
20 prospective look at risk, treatment, and outcome. The journal of maternal-fetal & neonatal
21
22 medicine : the official journal of the European Association of Perinatal Medicine, the
23
24 Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal
25
26 Obstet 2012;**25**(8):1488-93 doi: 10.3109/14767058.2011.644363[published Online First: Epub
27
28 Date]].
29
30
31
32 28. Laopaiboon M, Lumbiganon P, Intarut N, et al. Advanced maternal age and pregnancy outcomes: a
33
34 multicountry assessment. BJOG : an international journal of obstetrics and gynaecology
35
36 2014;**121 Suppl 1**:49-56 doi: 10.1111/1471-0528.12659[published Online First: Epub Date]].
37
38
39 29. Araya BM, Diaz M, Paredes D, Ortiz J. Association between preterm birth and its subtypes and
40
41 maternal sociodemographic characteristics during the post-transitional phase in a developing
42
43 country with a very high human development index. Public health 2017;**147**:39-46 doi:
44
45 10.1016/j.puhe.2017.01.027[published Online First: Epub Date]].
46
47
48
49 30. Chen X, Scholl TO. Association of elevated free fatty acids during late pregnancy with preterm
50
51 delivery. Obstetrics and gynecology 2008;**112**(2 Pt 1):297-303 doi:
52
53 10.1097/AOG.0b013e3181802150[published Online First: Epub Date]].
54
55
56
57
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59
60

- 1
2
3
4 31. Passini R, Jr., Cecatti JG, Lajos GJ, et al. Brazilian multicentre study on preterm birth (EMIP):
5
6 prevalence and factors associated with spontaneous preterm birth. PloS one
7
8 2014;**9**(10):e109069 doi: 10.1371/journal.pone.0109069[published Online First: Epub Date]].
9
10
11 32. Ovalle A, Kakarieka E, Rencoret G, et al. [Risk factors for preterm deliveries in a public hospital].
12
13 Revista medica de Chile 2012;**140**(1):19-29 doi: /S0034-98872012000100003[published
14
15 Online First: Epub Date]].
16
17
18 33. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth.
19
20 Lancet 2008;**371**(9606):75-84 doi: 10.1016/S0140-6736(08)60074-4[published Online First:
21
22 Epub Date]].
23
24
25
26 34. Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of
27
28 hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG : an
29
30 international journal of obstetrics and gynaecology 2011;**118**(11):1302-13 doi:
31
32 10.1111/j.1471-0528.2011.03023.x[published Online First: Epub Date]].
33
34
35
36 35. Schiff MA, Reed SD, Daling JR. The sex ratio of pregnancies complicated by hospitalisation for
37
38 hyperemesis gravidarum. BJOG : an international journal of obstetrics and gynaecology
39
40 2004;**111**(1):27-30
41
42
43
44 36. Lee J-I, Lee J-A, Lim H-S. Morning sickness reduces dietary diversity, nutrient intakes, and infant
45
46 outcome of pregnant women. Nutrition Research 2004;**24**(7):531-40 doi:
47
48 10.1016/j.nutres.2003.10.011[published Online First: Epub Date]].
49
50
51 37. Jarnfelt-Samsioe A, Eriksson B, Waldenstrom J, Samsioe G. Some new aspects on emesis
52
53 gravidarum. Relations to clinical data, serum electrolytes, total protein and creatinine.
54
55 Gynecologic and obstetric investigation 1985;**19**(4):174-86
56
57
58
59
60

- 1
2
3
4 38. Haugen M, Vikanes A, Brantsaeter AL, Meltzer HM, Grjibovski AM, Magnus P. Diet before
5 pregnancy and the risk of hyperemesis gravidarum. *The British journal of nutrition*
6 2011;**106**(4):596-602 doi: 10.1017/s0007114511000675[published Online First: Epub Date]].
7
8
9
10
11 39. Huxley RR. Nausea and vomiting in early pregnancy: its role in placental development. *Obstetrics*
12 and gynecology 2000;**95**(5):779-82
13
14
15
16 40. Girsen AI, Mayo JA, Carmichael SL, et al. Women's prepregnancy underweight as a risk factor for
17 preterm birth: a retrospective study. *BJOG : an international journal of obstetrics and*
18 *gynaecology* 2016;**123**(12):2001-07 doi: 10.1111/1471-0528.14027[published Online First:
19 Epub Date]].
20
21
22
23
24
25
26 41. Pan Y, Zhang S, Wang Q, et al. Investigating the association between prepregnancy body mass
27 index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant
28 women in rural China. *BMJ open* 2016;**6**(6):e011227 doi:
29 10.1136/bmjopen-2016-011227[published Online First: Epub Date]].
30
31
32
33
34
35
36 42. Koren G, Maltepe C, Navioz Y, Wolpin J. Recall bias of the symptoms of nausea and vomiting of
37 pregnancy. *American journal of obstetrics and gynecology* 2004;**190**(2):485-8 doi:
38 10.1016/j.ajog.2003.08.039[published Online First: Epub Date].
39
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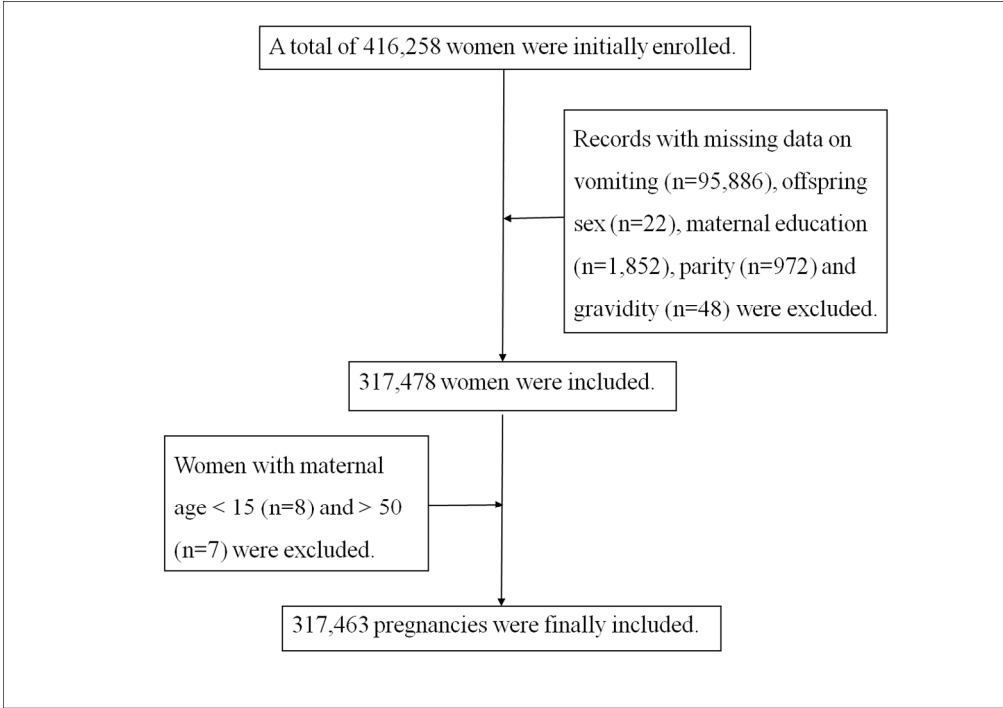
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Figure legends

Figure 1. Flow chart of population selection

For peer review only

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Table S1 Odds ratios (ORs) and 95% confidence intervals (CIs) for preterm birth in relation to maternal and infants' characteristics

	Pre-term n (%)	Full-term n (%)	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)*	<i>P</i> *
Age at delivery						
<25	3091 (3.62)	82224 (96.38)	0.69(0.66,0.72)	<0.001	0.79(0.76,0.83)	<0.001
25~34	11055 (5.17)	202692 (94.83)	1.00(Reference)		1.00(Reference)	
≥35	1743 (9.47)	16658 (90.53)	1.93(1.83,2.03)	<0.001	1.69(1.59,1.78)	<0.001
Education level						
Less than high school	3519 (4.55)	73737 (95.45)	0.97(0.925,1.01)	0.1339	0.91(0.87,0.95)	<0.001
High school	5010 (4.71)	101458 (95.29)	1.00(Reference)		1.00(Reference)	
College	7360 (5.50)	126379 (94.50)	1.18(1.14,1.22)	<0.001	1.16(1.12,1.21)	<0.001
Offspring sex						
Male	9188 (5.41)	160671 (94.59)	1.00(Reference)		1.00(Reference)	
Female	6701 (4.54)	140903 (95.46)	0.83(0.81,0.86)	<0.001	0.84(0.82,0.87)	<0.001
Parity						
Nullipara	11948 (4.65)	245121 (95.35)	1.00(Reference)		1.00(Reference)	
Multipara	3941 (6.55)	56453 (93.47)	1.4(1.38,1.49)	<0.001	1.14(1.09,1.20)	<0.001

Gravidity						
<3	11471 (4.59)	238259 (95.41)	1.00(Reference)		1.00(Reference)	
≥3	4418 (6.52)	63315 (93.48)	1.45(1.40,1.50)	<0.001	1.211(1.16,1.27)	<0.001
Pre-pregnancy BMI(kg/m²)						
Under weight (<18.5)	3118 (4.21)	70916 (95.79)	0.83(0.80,0.86)	<0.001	0.90(0.86,0.94)	<0.001
Normal (18.5~23.9)	11083 (5.03)	209246 (94.97)	1.00(Reference)		1.00(Reference)	
Overweight(24~27.9)	1360 (6.94)	18226 (93.06)	1.41(1.33,1.50)	<0.001	1.32(1.25,1.40)	<0.001
Obese(≥28)	328 (9.33)	3186 (90.67)	1.96(1.75,2.20)	<0.001	1.86,1.66,2.09)	<0.001
Vomiting						
Yes	4978 (5.25)	89879 (94.75)	1.08(1.04, 1.11)		1.05(1.02, 1.09)	
No	10911 (4.90)	211695 (95.10)	1.00(Reference)	<0.001	1.00(Reference)	0.0048

* Age at delivery, educational level, offspring sex, parity, gravidity, pre-pregnancy BMI, and vomiting in the first trimester were mutually adjusted.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	No. of Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	NR
		(e) Describe any sensitivity analyses	NR
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8-9

1		which confounders were adjusted for and why they were included	
2		(b) Report category boundaries when continuous variables were	8
3		categorized	
4		(c) If relevant, consider translating estimates of relative risk into absolute	9
5		risk for a meaningful time period	
6			
7	Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions,	9
8		and sensitivity analyses	
9			
10	Discussion		
11	Key results	18 Summarise key results with reference to study objectives	10-11
12	Limitations	19 Discuss limitations of the study, taking into account sources of potential	
13		bias or imprecision. Discuss both direction and magnitude of any potential	
14		bias	
15			
16	Interpretation	20 Give a cautious overall interpretation of results considering objectives,	12
17		limitations, multiplicity of analyses, results from similar studies, and other	
18		relevant evidence	
19			
20	Generalisability	21 Discuss the generalisability (external validity) of the study results	12
21			
22	Other information		
23	Funding	22 Give the source of funding and the role of the funders for the present study	13
24		and, if applicable, for the original study on which the present article is	
25		based	
26			

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Association between vomiting in the first trimester and preterm birth: a retrospective birth cohort study in Wuhan, China

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-017309.R3
Article Type:	Research
Date Submitted by the Author:	12-Aug-2017
Complete List of Authors:	<p>Hu, Ronghua; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Chen, Yawen; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Zhang, Yiming; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Qian, Zhengmin ; Saint Louis University, Department of Epidemiology, School of Public Health</p> <p>Liu, Yan; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Vaughn, MG; Saint Louis University, School of Social Work</p> <p>Xu, Shunqing; Tongji Medical College, Huazhong University of Science and Technology, Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health, School of Public Health</p> <p>Zheng, Tongzhang; Brown University, Department of Epidemiology, School of Public Health</p> <p>Liu, Mingzhu; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p> <p>Zhang, Bin; Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science and Technology</p>
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	vomiting, preterm birth, pre-pregnancy body mass index

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**Association between vomiting in the first trimester and preterm birth:
a retrospective birth cohort study in Wuhan, China**

Ronghua Hu^{1§}, Yawen Chen^{1§}, Yiming Zhang¹, Zhengmin Qian², Yan Liu¹, Michael
G. Vaughn², Shunqing Xu³, Tongzhang Zheng⁴, Mingzhu Liu¹, Bin Zhang^{1*}

¹ Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, Hubei,
People's Republic of China

² Department of Epidemiology, College for Public Health and Social Justice, Saint
Louis University, MO, United States of America

³ Key Laboratory of Environment and Health, School of Public Health, Tongji
Medical College, Huazhong University of Science and Technology, Wuhan, Hubei,
People's Republic of China

⁴ Department of Epidemiology, School of Public Health, Providence, Brown
University, RI, United States of America

[§] These authors contributed equally to this work

***Corresponding author**

Full name: Bin Zhang

Postal address: No.100 Hongkong Road, Wuhan 430014, Hubei, China,

E-mail: mchwhzb@163.com

Telephone and fax number: +86-027-82433149

Abstract

Objective: Although vomiting in the first trimester has been reported to be associated with preterm birth (PTB), findings supporting this association remain inconsistent. Our aim was to assess the association between vomiting and PTB, as well as evaluate if the association is modified by pre-pregnancy body mass index (BMI).

Design: A retrospective cohort study.

Setting: Wuhan, a central city of China.

Participants: A total of 317,463 pregnant women who had a live, singleton newborn from January 1, 2010, to May 23, 2016 were enrolled in our study.

Main outcome measure: PTB was defined as gestational age <37 gestational weeks. Gestational age was calculated using reports from mothers based on the first day of their last menstrual period. An ultrasound was routinely used to determine gestational age before 12 gestational weeks.

Results: Of the 317,463 pregnant women, 29.88% (94,857) experienced vomiting in the first trimester and 5.00% (15,889) experienced a PTB. Vomiting in the first trimester increased the risk for PTB and the multivariable adjusted odds ratio (OR) was 1.05 (95% confidence interval (CI) = 1.02~1.09). In the stratified analyses, the association of vomiting in the first trimester was significant among underweight women (adjusted OR=1.08, 95%CI=1.04~1.17) and normal pre-pregnancy BMI women (adjusted OR=1.06, 95%CI=1.02~1.11), but not in overweight women (adjusted OR=1.01, 95% CI=0.90~1.14) and obese women (adjusted OR=0.93, 95% CI=0.73~1.19).

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4 **Conclusions:** Our study indicates that vomiting in the first trimester was associated
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6 with PTB. Additionally, women with underweight and normal pre-pregnancy BMI
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8 that experienced vomiting are more likely to have a PTB.
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11 **Keywords:** vomiting; preterm birth; pre-pregnancy body mass index
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14 15 16 **Strengths and limitations of this study** 17

- 18 1. The present study is a cohort study enrolled a large population of 317,463 pregnant
19 women.
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- 22 2. This is the first study exploring the relationship between vomiting in the first
23 trimester and PTB in Chinese women by pre-pregnancy BMI status.
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- 26 3. Vomiting symptoms was based on self-reported, which may be a possible source of
27 bias.
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- 30 4. The prevalence of overweight and obesity were relatively low in our sample, and
31 the relationship between vomiting and PTB in women with a high pre-pregnancy BMI
32 needs to be further assessed.
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Introduction

Nausea and vomiting in pregnancy (NVP) is a collection of symptoms composed of nausea alone, or nausea in combination with vomiting.[1] This condition typically starts prior to 9 weeks of gestation and subsides by the end of the first trimester; however, this condition has been shown to continue into the second trimester in up to 25% of pregnant women and for 0.3-2.3% into the third trimester.[2] NVP has an important effect on both individuals and society as it causes emotional distress, depression, and can have a negative effect on a woman's activities and relationships.[3 4] NVP also has been found to lead to loss of time at work and a decrease in job productivity.[5] The etiology of NVP remains unknown, although it is currently believed to be related to early pregnancy hormones.[6]

Almost 70% of women worldwide experience NVP.[7] The average rate of vomiting only in early pregnancy is 47.1%, and the reported rates generally range from 22.3% to 63.5%.[8] A Norwegian cohort investigation reported that the rate of NVP was 33% among 51,675 women.[9] Källén et al. studied the occurrence of NVP via questionnaires in 3,675 Swedish pregnant women and observed that 38.3% of pregnant women reported vomiting in early pregnancy.[10] One previous meta-analysis, which included 23 studies comprised of 67,602 women,[11] estimated the rate of NVP in the USA to be as high as 68.6%. Meanwhile, studies on the rate of NVP in China are few and are limited by their small sample sizes. Chin et al.[12] conducted a study in a district hospital in Hong Kong in 1989 and found that the incidence of NVP was 74.9% among 1,453 patients. Another cross-sectional study

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4 conducted in a University obstetric unit in Hong Kong revealed that the prevalence of
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6 NVP was 90.9% among 396 women.[13]
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9 In previous studies, NVP was not found to be associated with primary maternal
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11 diseases such as gastrointestinal infections or allergies.[8] Recently there was a
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13 resurgence of interest in topics related to NVP, such as death,[14] pregnancy
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15 complications,[15] and birth outcomes.[16] Some studies reported that women with
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17 NVP were more likely to have a preterm birth (PTB) compared with symptom- free
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19 women.[15 17 18] Still, other studies have found no association between this
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21 phenomenon.[6 19] However, Czeizel and Puho have suggested that women with
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23 NVP had a lower risk of PTB.[20] A Norway prospective cohort study involving
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25 51,675 pregnant women found nausea to decrease the risk for PTB by 14% but did not
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27 find NVP associated with PTB.[9]
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34 To our knowledge, there has been only one case-control study, which was
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36 conducted in Chinese pregnant women that addressed the relationship between PTB
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38 and a severe form of NVP called *Hyperemesis Gravidarum*. [19] Information about the
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40 association between vomiting in the first trimester and risk of PTB in China is unclear.
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42 Furthermore, there has not been a study in which the population was grouped
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44 according to pre-pregnancy BMI to determine its contribution to the identification of
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46 the association between NVP and risk of PTB. Thus, our objective in the present study
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48 is to explore the association between vomiting in the first trimester and PTB as well
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50 as assess whether pre-pregnancy BMI modifies this association using a birth cohort
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52 study in Wuhan, China.
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Materials and methods

Study population

A retrospective cohort study was conducted in Wuhan China, utilizing data from the Wuhan Maternal and Child Health Management Information System (WMCHMIS). The WMCHMIS was introduced in our previous study.[21] Enrolled women included every pregnant woman who had a live, singleton newborn from January 1, 2010, to May 23, 2016. The study has been approved by the Wuhan Medical and Healthcare Center for Women and Children.

A total of 416,258 women were initially enrolled. We then excluded records with missing data on vomiting (n=95,886), offspring sex (n=22), maternal education (n=1,852), parity (n=972), and gravidity (n=48). Moreover, we also excluded those with a maternal age less than 15 (n=8) and more than 50 (n=7). The final study population consisted of 317,463 pregnancies or 76.27% of the initial population.

Variables

Vomiting in the first trimester was assessed when pregnant women first visited the women and children healthcare centers. Maternal age, education, parity, gravidity, pre-pregnancy weight, and height were self-reported at their first antenatal care visit while offspring sex and other obstetric information were provided by midwives documented in WMCHMIS. Information was audited by clinicians and obstetric nurses, and a warning would be activated when illogical data were input into WMCHMIS.

Vomiting was dichotomized into yes and no response formats. Maternal age was

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4 categorized into 3 groups: younger than 25, 25~34 years old, and 35 years old and
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6 older. A proxy for socioeconomic status was the maternal education which was
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8 categorized into 3 groups: less than high school, high school, and college. By parity,
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10 women were dichotomized into nullipara and multipara. Regarding gravidity, it was
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12 divided into less than 3 times and 3 times and more. Pre-pregnancy BMI was
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14 calculated as $\text{weight}/\text{height}^2$ and grouped into 4 categories according to Chinese
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16 standard of weight for adults.[22]
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21 The main outcome variable was PTB. PTB was defined as gestational age <37
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23 gestational weeks.[23] Gestational age was calculated using reports from mothers
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25 based on the first day of their last menstrual period. An ultrasound was routinely used
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27 to determine gestational age before 12 gestational weeks.
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30 31 *Statistical analysis*

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33 Results were presented as frequencies (%). Difference between PTB group and
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35 full-term group were assessed by Chi-square tests. A logistic regression model was
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37 used to estimate the association between vomiting in the first trimester and PTB.
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39 Results were adjusted for confounders including maternal age, education, parity,
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41 gravidity, pre-pregnancy BMI, and offspring sex in accord with previous studies.[9 24]
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43 We also employed a stratified analysis by pre-pregnancy BMI and the confounders
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45 adjusted in stratified analysis were maternal age, education, parity, gravidity, and
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47 offspring sex. Crude and adjusted odds ratios (ORs) statistics, as well as a 95%
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49 confidence interval (CI) were calculated. All statistical analyses were performed using
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51 SAS version 9.2 (SAS Statistical Institute, Inc., Cary, NC).
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Results

In 317,463 pregnancies included in our study (Figure 1), gestational age ranged from 28 weeks to 43 weeks. Altogether, 94,857 out of 317,463 pregnant women (29.88%) reported vomiting in the first trimester. And 5.00% (15,889) of the births were delivered preterm. Maternal demographics and characteristics are shown in Table 1. Women who were older than 35 years old, had a college education, were multipara, had more than 3 times gravidity, or had a higher pre-pregnancy BMI were more likely to have a PTB. PTB was observed to be more common in female babies than in male offspring.

Table 1. Characteristics of women and infants

	Preterm (n=15,889, 5.00%)		Full-term (n=301,574, 95.00%)		P
	n	%	n	%	
Age at delivery					
<25	3091	3.62	82224	96.38	
25~34	11055	5.17	202692	94.83	<0.001
≥35	1743	9.47	16658	90.53	
Education level					
Less than high school	3519	4.55	73737	95.45	
High school	5010	4.71	101458	95.29	<0.001
College	7360	5.50	126379	94.50	
Offspring sex					
Male	9188	5.41	160671	94.59	
Female	6701	4.54	140903	95.46	<0.001
Parity					
Nullipara	11948	4.65	245121	95.35	
Multipara	3941	6.53	56453	93.47	<0.001
Gravidity					
<3	11471	4.59	238259	95.41	
≥3	4418	6.52	63315	93.48	<0.001
Pre-pregnancy BMI(kg/m²)					

Underweight (<18.5)	3118	4.21	70916	95.79	
Normal (18.5~23.9)	11083	5.03	209246	94.97	<0.001
Overweight(24~27.9)	1360	6.94	18226	93.06	
Obese(\geq 28)	328	9.33	3186	90.67	
Vomiting					
Yes	4978	5.25	89879	94.75	<0.001
No	10911	4.90	211695	95.10	

When vomiting women were compared with non-vomiting women, we found that vomiting in the first trimester produced a significant increase in risk for PTB, with OR=1.08 and 95% CI=1.04~1.13. The relationship still persisted (OR=1.05, 95% CI=1.02~1.09, Table 2) after adjustment for aforementioned confounders. In the additional stratified analyses, the results showed that vomiting in the first trimester was associated with PTB in underweight women (OR=1.08, 95%CI=1.04~1.17) and in women with a normal pre-pregnancy BMI (OR=1.06, 95%CI=1.02~1.11), but not among overweight and obese groups. After adjusting for the same set of confounders, no changes occurred in the results (Table 2).

Table 2 Association between vomiting and PTB and its association stratified by pre-pregnancy BMI

	Pre-term n (%)	Full-term n (%)	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)*	<i>P</i>
Vomiting						
Yes	4978(5.25)	89879(94.75)	1.08(1.04, 1.11)	<0.001	1.05(1.02, 1.09)	0.0048^a
No	10911(4.90)	211695(95.10)	1.00		1.00	
Underweight						
Vomiting						
Yes	810(4.49)	17216(95.56)	1.08(1.05,1.17)	0.0042	1.08(1.04,1.17)	0.0082^b
No	2308(4.12)	53700(95.86)	1.00		1.00	
Normal						
Vomiting						
Yes	3610(5.22)	65485(94.78)	1.06(1.04,1.11)	0.0048	1.06(1.02,1.01)	0.0058^b

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No	7473(4.94)	143761(95.06)	1.00		1.00	
Overweight						
Vomiting						
Yes	462(7.04)	6099(92.96)	1.02(0.91,1.15)	0.7012	1.01(0.90,1.14)	0.8547 ^b
No	898(6.89)	12127(93.11)	1.00		1.00	
Obese						
Vomiting						
Yes	106(8.95)	1079(91.05)	0.93(0.73,1.19)	0.5719	0.93(0.73,1.19)	0.5508 ^b
No	222(9.53)	2107(90.47)	1.00		1.00	

OR: odds ratio; CI: confidence interval.

^a Adjusted for maternal age, education, parity, gravidity, pre-pregnancy BMI, and offspring sex;

^b Adjusted for maternal age, education, parity, gravidity, and offspring sex.

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).

Discussion

Nausea and vomiting (NVP) while pregnant has far reaching effects on the mental and physical health of mothers and their offspring. Little research has accrued on the association between NVP and PTB in China, especially taking into account pre-pregnancy BMI. This study showed that nearly 30% of Chinese pregnant women had experienced vomiting in the first trimester. The rate of vomiting in Chinese women was somewhat different than in other studies.[9 11 25-27] A Norwegian cohort study reported that the rate of NVP was 33% among 51,675 women with 15 gestational weeks,[9] which was higher than our findings. A previous meta-analysis estimated the rate of NVP in the USA was 68.6% including 23 studies composed of 67,602 women.[11] Conflicting results can likely be explained by heterogeneity of

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4 populations, methods, definitions and confounders.

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6 Our results showed that socio-demographic factors, such as age, education level,
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8 parity, and gravidity, might influence PTB. Previous studies have indicated that
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10 women with advanced maternal age were associated with increased risk of PTB.[28
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12 29] Araya BM et al. reported that age >35 years, delivery of more than two fetuses,
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14 and <8 years of education were risks factors for PTB.[29] Women aged >35 had
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16 longer exposure times to chronic pathologies and unhealthy lifestyles,[30] and higher
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18 prevalence of maternal obesity in older mothers, which were associated with risks
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20 factors for PTB.[31] Several studies demonstrated that the lower the socio-economic
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22 and education level, the higher the probability of developing infection, and that was
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24 clearly associated with PTB before 30 weeks of gestation.[32 33]
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31 In this large cohort study conducted among Chinese women, we have found an
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33 association between vomiting in the first trimester and PTB before 37 weeks of
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35 gestation. When compared with non-vomiting pregnant women, women that
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37 experienced vomiting were at an increased risk of PTB. Our results were inconsistent
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39 with that of other studies.[15 18 34 35] For example, Andrew and Puho indicated that
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41 there was a significant association of vomiting with a decreased risk of PTB,[20] and
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43 Naumann et al. found that vomiting was not associated with PTB.[27] The differences
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45 found among these studies may be attributed to race, definition or classification of
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47 vomiting, and the differential sample sizes of the populations mentioned above.
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53 The possible causal link between vomiting and PTB remains elusive. The most
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55 common hypothesis proffered to explain the harmful effects of vomiting is based on
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4 the fact that vomiting leads to abnormal digestive function, which results in a lower
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6 nutrient intake of pregnant women.[14 36] Vomiting may also affect maternal and
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8 fetal physiology through dehydration and the modulation of stress-related risk
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10 factors.[37 38] Moreover, vomiting may cause low maternal weight gain during
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12 pregnancy, which has been associated with PTB as reported by Canadian research.[6]
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16 Additionally, our results reveal that vomiting was a risk factor for PTB in women
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18 with underweight and normal pre-pregnancy BMI, but not in overweight and obese
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20 women. Previous studies have estimated the risk factors for vomiting and PTB
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22 separately and found different effects of pre-pregnancy BMI on vomiting and
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24 PTB.[39-41] No study has assessed the association between vomiting and PTB by
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26 pre-pregnancy BMI. The biological mechanisms underlying the associations with
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28 maternal pre-pregnancy BMIs remain unclear. Gary et al. indicated that the
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30 relationship between pre-pregnancy BMI and risk of PTB were complex.[23]
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32 Although it was not statistically significant, a trend towards lower risk for PTB in
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34 obese women with vomiting was observed. We speculate that vomiting may have
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36 relatively few impacts on the nutrition of obese women due to their increased
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38 capacity for energy storage.
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47 Strengths of this study are as follows. First, this is the first study exploring the
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49 relationship between vomiting in the first trimester and PTB in Chinese women while
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51 assessing the association between PTB and vomiting by pre-pregnancy BMI status.
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54 Second, the data were collected from the large population-based cohort and linked to
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56 the WMCHMIS, providing thorough and detailed access to pregnancy and birth
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4 outcomes. Third, with such a large cohort size, many significant associations tend to
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6 appear, and the merit of these in the clinical setting is notable. However, there are two
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8 limitations. One is the reliance on self-reported data on vomiting. Retrospective
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10 evaluation of vomiting symptoms has been reported as a possible source of bias.[42]
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12 The other is that the prevalence of overweight and obesity were relatively low in our
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14 sample (6.17% and 1.10%, respectively) and the relationship between vomiting and
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16 PTB in women with a high pre-pregnancy BMI needs to be further assessed.
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20 21 **Conclusion**

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23 This study showed that vomiting presented an increased risk for PTB based on a large
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25 cohort study in China, although the effect was small. Vomiting was a risk for PTB in
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27 women who were underweight and normal weight based on their pre-pregnancy BMI.
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29 Although no significant association between vomiting and PTB in overweight and
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31 obese women was observed, clinicians should give all women suitable guidance for
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33 dealing with vomiting to ensure improved pregnancy outcomes. Finally, we recognize
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35 the need for greater clarity with respect to the association between vomiting and PTB
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37 and encourage researchers to build on our findings.
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43 44 **Acknowledgement**

45
46 We are extremely grateful to all the families who took part in this study, the staff of
47
48 the Wuhan Health Bureau, and all the hospitals and community health centers
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50 involved in this study.
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53 54 **Ethics approval**

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56 The Institutional Review Board of Wuhan Medical and Healthcare Center for Women
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4 and Children received and approved this study (approved on 10/13/2016).

5
6 **Funding**

7
8 None.

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11 **Patient consent**

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13 Obtained.

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16 **Competing interests**

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18 None declared.

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21 **Data sharing statement**

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23 No additional data are available.

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26 **Contribution to authorship**

27
28 RHH, YWC, BZ designed the research; YWC, YMZ, MZL analyzed data; RHH,
29
30 YWC, YL drafted the manuscript; ZMQ, MGW, SQX, TZZ, BZ revised the
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32 manuscript.
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39 **References**

- 40
41 1. Flaxman SM, Sherman PW. Morning sickness: a mechanism for protecting mother and embryo. The
42
43 Quarterly review of biology 2000;**75**(2):113-48
44
45
46 2. Koren G, Madjunkova S, Maltepe C. The protective effects of nausea and vomiting of pregnancy
47
48 against adverse fetal outcome--a systematic review. Reproductive toxicology 2014;**47**:77-80
49
50 doi: 10.1016/j.reprotox.2014.05.012[published Online First: Epub Date].
51
52
53 3. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during
54
55 pregnancy. The British journal of general practice : the journal of the Royal College of
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56
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59
60
- General Practitioners 1993;**43**(371):245-8
4. Mazzotta P, Maltepe C, Navioz Y, Magee LA, Koren G. Attitudes, management and consequences of nausea and vomiting of pregnancy in the United States and Canada. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics* 2000;**70**(3):359-65
5. Smith C, Crowther C, Beilby J, Dandeaux J. The impact of nausea and vomiting on women: a burden of early pregnancy. *The Australian & New Zealand journal of obstetrics & gynaecology* 2000;**40**(4):397-401
6. Dodds L, Fell DB, Joseph KS, Allen VM, Butler B. Outcomes of pregnancies complicated by hyperemesis gravidarum. *Obstetrics and gynecology* 2006;**107**(2 Pt 1):285-92 doi: 10.1097/01.AOG.0000195060.22832.cd[published Online First: Epub Date]].
7. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. *Journal of population therapeutics and clinical pharmacology = Journal de la therapeutique des populations et de la pharamcologie clinique* 2013;**20**(2):e171-83
8. Koch KL, Frissora CL. Nausea and vomiting during pregnancy. *Gastroenterology clinics of North America* 2003;**32**(1):201-34, vi
9. Chortatos A, Haugen M, Iversen PO, et al. Pregnancy complications and birth outcomes among women experiencing nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study. *BMC Pregnancy Childbirth* 2015;**15**:138 doi: 10.1186/s12884-015-0580-6[published Online First: Epub Date]].
10. Kallen B, Lundberg G, Aberg A. Relationship between vitamin use, smoking, and nausea and vomiting of pregnancy. *Acta obstetricia et gynecologica Scandinavica* 2003;**82**(10):916-20

- 1
2
3
4 11. Einarson TR, Piwko C, Koren G. Prevalence of nausea and vomiting of pregnancy in the USA: a
5
6 meta analysis. *Journal of population therapeutics and clinical pharmacology = Journal de la*
7
8 *therapeutique des populations et de la pharmacologie clinique* 2013;**20**(2):e163-70
9
10
- 11 12. Chin RK. Antenatal complications and perinatal outcome in patients with nausea and
12
13 vomiting-complicated pregnancy. *European journal of obstetrics, gynecology, and*
14
15 *reproductive biology* 1989;**33**(3):215-9
16
17
- 18 13. Chan OK, Sahota DS, Leung TY, Chan LW, Fung TY, Lau TK. Nausea and vomiting in
19
20 health-related quality of life among Chinese pregnant women. *The Australian & New Zealand*
21
22 *journal of obstetrics & gynaecology* 2010;**50**(6):512-8 doi:
23
24 10.1111/j.1479-828X.2010.01216.x[published Online First: Epub Date]].
25
26
- 27 14. Birkeland E, Stokke G, Tangvik RJ, et al. Norwegian PUQE (Pregnancy-Unique Quantification of
28
29 Emesis and nausea) identifies patients with hyperemesis gravidarum and poor nutritional
30
31 intake: a prospective cohort validation study. *PloS one* 2015;**10**(4):e0119962 doi:
32
33 10.1371/journal.pone.0119962[published Online First: Epub Date]].
34
35
- 36 15. Roseboom TJ, Ravelli AC, van der Post JA, Painter RC. Maternal characteristics largely explain
37
38 poor pregnancy outcome after hyperemesis gravidarum. *European journal of obstetrics,*
39
40 *gynecology, and reproductive biology* 2011;**156**(1):56-9 doi:
41
42 10.1016/j.ejogrb.2011.01.010[published Online First: Epub Date]].
43
44
- 45 16. Chan RL, Olshan AF, Savitz DA, et al. Severity and duration of nausea and vomiting symptoms in
46
47 pregnancy and spontaneous abortion. *Human reproduction* 2010;**25**(11):2907-12 doi:
48
49 10.1093/humrep/deq260[published Online First: Epub Date]].
50
51
- 52 17. Paauw JD, Bierling S, Cook CR, Davis AT. Hyperemesis gravidarum and fetal outcome. *JPEN.*
53
54
55
56
57
58
59
60

- Journal of parenteral and enteral nutrition 2005;**29**(2):93-6
18. Temming L, Franco A, Istwan N, et al. Adverse pregnancy outcomes in women with nausea and vomiting of pregnancy. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet 2014;**27**(1):84-8 doi: 10.3109/14767058.2013.806473[published Online First: Epub Date]].
19. Zhang J, Cai WW. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes. Epidemiology 1991;**2**(6):454-7
20. Czeizel AE, Puho E. Association between severe nausea and vomiting in pregnancy and lower rate of preterm births. Paediatric and perinatal epidemiology 2004;**18**(4):253-9 doi: 10.1111/j.1365-3016.2004.00568.x[published Online First: Epub Date]].
21. Zhou A, Xiong C, Hu R, et al. Pre-Pregnancy BMI, Gestational Weight Gain, and the Risk of Hypertensive Disorders of Pregnancy: A Cohort Study in Wuhan, China. PloS one 2015;**10**(8):e0136291 doi: 10.1371/journal.pone.0136291[published Online First: Epub Date]].
22. Wang Y, Mi J, Shan XY, Wang QJ, Ge KY. 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]].
23. 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[published Online First: Epub Date]].
24. Vikanes AV, Stoer NC, Magnus P, Grjibovski AM. Hyperemesis gravidarum and pregnancy

- 1
2
3
4 outcomes in the Norwegian Mother and Child Cohort - a cohort study. BMC pregnancy and
5
6 childbirth 2013;**13**:169 doi: 10.1186/1471-2393-13-169[published Online First: Epub Date]].
7
8
9 25. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy.
10
11 Obstetrics and gynecology 1985;**66**(5):612-6
12
13
14 26. Tierson FD, Olsen CL, Hook EB. Nausea and vomiting of pregnancy and association with
15
16 pregnancy outcome. American journal of obstetrics and gynecology 1986;**155**(5):1017-22
17
18
19 27. Naumann CR, Zelig C, Napolitano PG, Ko CW. Nausea, vomiting, and heartburn in pregnancy: a
20
21 prospective look at risk, treatment, and outcome. The journal of maternal-fetal & neonatal
22
23 medicine : the official journal of the European Association of Perinatal Medicine, the
24
25 Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal
26
27 Obstet 2012;**25**(8):1488-93 doi: 10.3109/14767058.2011.644363[published Online First: Epub
28
29 Date]].
30
31
32
33
34 28. Laopaiboon M, Lumbiganon P, Intarut N, et al. Advanced maternal age and pregnancy outcomes: a
35
36 multicountry assessment. BJOG : an international journal of obstetrics and gynaecology
37
38 2014;**121 Suppl 1**:49-56 doi: 10.1111/1471-0528.12659[published Online First: Epub Date]].
39
40
41 29. Araya BM, Diaz M, Paredes D, Ortiz J. Association between preterm birth and its subtypes and
42
43 maternal sociodemographic characteristics during the post-transitional phase in a developing
44
45 country with a very high human development index. Public health 2017;**147**:39-46 doi:
46
47 10.1016/j.puhe.2017.01.027[published Online First: Epub Date]].
48
49
50
51 30. Chen X, Scholl TO. Association of elevated free fatty acids during late pregnancy with preterm
52
53 delivery. Obstetrics and gynecology 2008;**112**(2 Pt 1):297-303 doi:
54
55 10.1097/AOG.0b013e3181802150[published Online First: Epub Date]].
56
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59
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2
3
4 31. Passini R, Jr., Cecatti JG, Lajos GJ, et al. Brazilian multicentre study on preterm birth (EMIP):
5
6 prevalence and factors associated with spontaneous preterm birth. PloS one
7
8 2014;**9**(10):e109069 doi: 10.1371/journal.pone.0109069[published Online First: Epub Date]].
9
10
11 32. Ovalle A, Kakarieka E, Rencoret G, et al. [Risk factors for preterm deliveries in a public hospital].
12
13 Revista medica de Chile 2012;**140**(1):19-29 doi: /S0034-98872012000100003[published
14
15 Online First: Epub Date]].
16
17
18 33. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth.
19
20 Lancet 2008;**371**(9606):75-84 doi: 10.1016/S0140-6736(08)60074-4[published Online First:
21
22 Epub Date]].
23
24
25
26 34. Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of
27
28 hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG : an
29
30 international journal of obstetrics and gynaecology 2011;**118**(11):1302-13 doi:
31
32 10.1111/j.1471-0528.2011.03023.x[published Online First: Epub Date]].
33
34
35
36 35. Schiff MA, Reed SD, Daling JR. The sex ratio of pregnancies complicated by hospitalisation for
37
38 hyperemesis gravidarum. BJOG : an international journal of obstetrics and gynaecology
39
40 2004;**111**(1):27-30
41
42
43
44 36. Lee J-I, Lee J-A, Lim H-S. Morning sickness reduces dietary diversity, nutrient intakes, and infant
45
46 outcome of pregnant women. Nutrition Research 2004;**24**(7):531-40 doi:
47
48 10.1016/j.nutres.2003.10.011[published Online First: Epub Date]].
49
50
51 37. Jarnfelt-Samsioe A, Eriksson B, Waldenstrom J, Samsioe G. Some new aspects on emesis
52
53 gravidarum. Relations to clinical data, serum electrolytes, total protein and creatinine.
54
55 Gynecologic and obstetric investigation 1985;**19**(4):174-86
56
57
58
59
60

- 1
2
3
4 38. Haugen M, Vikanes A, Brantsaeter AL, Meltzer HM, Grjibovski AM, Magnus P. Diet before
5 pregnancy and the risk of hyperemesis gravidarum. *The British journal of nutrition*
6 2011;**106**(4):596-602 doi: 10.1017/s0007114511000675[published Online First: Epub Date]].
7
8
9
10
11 39. Huxley RR. Nausea and vomiting in early pregnancy: its role in placental development. *Obstetrics*
12 and gynecology 2000;**95**(5):779-82
13
14
15 40. Girsen AI, Mayo JA, Carmichael SL, et al. Women's prepregnancy underweight as a risk factor for
16 preterm birth: a retrospective study. *BJOG : an international journal of obstetrics and*
17 gynaecology 2016;**123**(12):2001-07 doi: 10.1111/1471-0528.14027[published Online First:
18 Epub Date]].
19
20
21
22
23
24
25 41. Pan Y, Zhang S, Wang Q, et al. Investigating the association between prepregnancy body mass
26 index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant
27 women in rural China. *BMJ open* 2016;**6**(6):e011227 doi:
28 10.1136/bmjopen-2016-011227[published Online First: Epub Date]].
29
30
31
32
33
34
35 42. Koren G, Maltepe C, Navioz Y, Wolpin J. Recall bias of the symptoms of nausea and vomiting of
36 pregnancy. *American journal of obstetrics and gynecology* 2004;**190**(2):485-8 doi:
37 10.1016/j.ajog.2003.08.039[published Online First: Epub Date].
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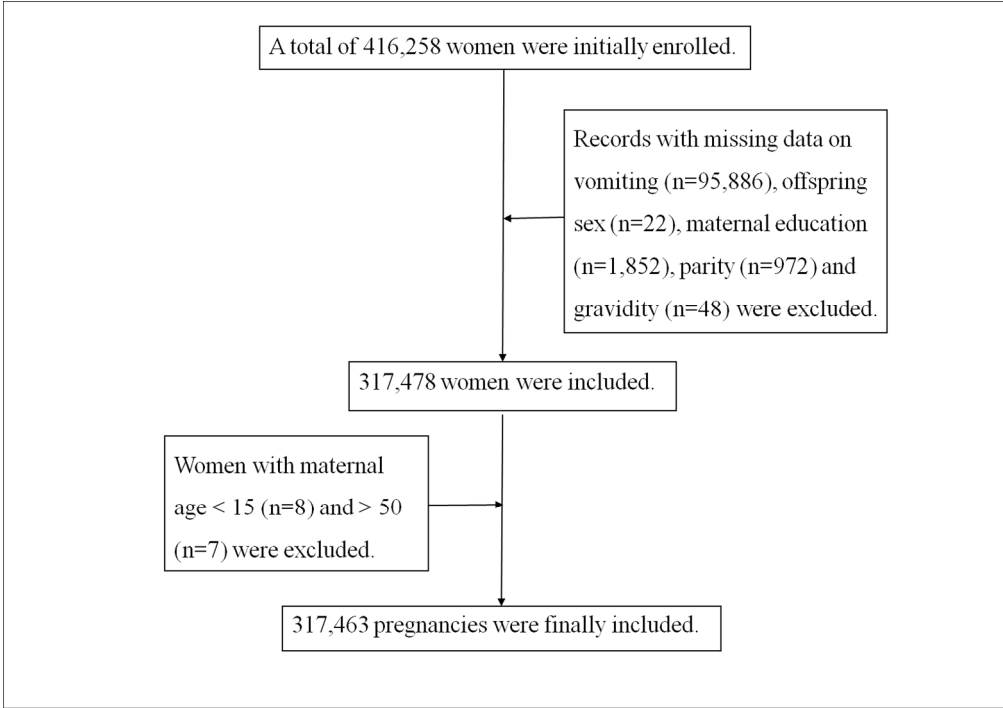
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Figure legends

Figure 1. Flow chart of population selection

For peer review only

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Table S1 Odds ratios (ORs) and 95% confidence intervals (CIs) for preterm birth in relation to maternal and infants' characteristics

	Pre-term n (%)	Full-term n (%)	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)*	<i>P</i> *
Age at delivery						
<25	3091 (3.62)	82224 (96.38)	0.69(0.66,0.72)	<0.001	0.79(0.76,0.83)	<0.001
25~34	11055 (5.17)	202692 (94.83)	1.00(Reference)		1.00(Reference)	
≥35	1743 (9.47)	16658 (90.53)	1.93(1.83,2.03)	<0.001	1.69(1.59,1.78)	<0.001
Education level						
Less than high school	3519 (4.55)	73737 (95.45)	0.97(0.925,1.01)	0.1339	0.91(0.87,0.95)	<0.001
High school	5010 (4.71)	101458 (95.29)	1.00(Reference)		1.00(Reference)	
College	7360 (5.50)	126379 (94.50)	1.18(1.14,1.22)	<0.001	1.16(1.12,1.21)	<0.001
Offspring sex						
Male	9188 (5.41)	160671 (94.59)	1.00(Reference)		1.00(Reference)	
Female	6701 (4.54)	140903 (95.46)	0.83(0.81,0.86)	<0.001	0.84(0.82,0.87)	<0.001
Parity						
Nullipara	11948 (4.65)	245121 (95.35)	1.00(Reference)		1.00(Reference)	
Multipara	3941 (6.55)	56453 (93.47)	1.4(1.38,1.49)	<0.001	1.14(1.09,1.20)	<0.001

Gravidity

<3	11471 (4.59)	238259 (95.41)	1.00(Reference)		1.00(Reference)	
≥3	4418 (6.52)	63315 (93.48)	1.45(1.40,1.50)	<0.001	1.211(1.16,1.27)	<0.001

Pre-pregnancy

BMI(kg/m²)

Under weight (<18.5)	3118 (4.21)	70916 (95.79)	0.83(0.80,0.86)	<0.001	0.90(0.86,0.94)	<0.001
Normal (18.5~23.9)	11083 (5.03)	209246 (94.97)	1.00(Reference)		1.00(Reference)	
Overweight(24~27.9)	1360 (6.94)	18226 (93.06)	1.41(1.33,1.50)	<0.001	1.32(1.25,1.40)	<0.001
Obese(≥28)	328 (9.33)	3186 (90.67)	1.96(1.75,2.20)	<0.001	1.86,1.66,2.09)	<0.001

Vomiting

Yes	4978 (5.25)	89879 (94.75)	1.08(1.04, 1.11)		1.05(1.02, 1.09)	
No	10911 (4.90)	211695 (95.10)	1.00(Reference)	<0.001	1.00(Reference)	0.0048

* Age at delivery, educational level, offspring sex, parity, gravidity, pre-pregnancy BMI, and vomiting in the first trimester were mutually adjusted.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	No. of Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7
		(b) Describe any methods used to examine subgroups and interactions	7
		(c) Explain how missing data were addressed	6
		(d) If applicable, explain how loss to follow-up was addressed	NR
		(e) Describe any sensitivity analyses	NR
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	8
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8-9

1		which confounders were adjusted for and why they were included	
2		(b) Report category boundaries when continuous variables were	8
3		categorized	
4		(c) If relevant, consider translating estimates of relative risk into absolute	9
5		risk for a meaningful time period	
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7	Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions,	9
8		and sensitivity analyses	
9			
10	Discussion		
11	Key results	18 Summarise key results with reference to study objectives	10-11
12	Limitations	19 Discuss limitations of the study, taking into account sources of potential	
13		bias or imprecision. Discuss both direction and magnitude of any potential	
14		bias	
15			
16	Interpretation	20 Give a cautious overall interpretation of results considering objectives,	12
17		limitations, multiplicity of analyses, results from similar studies, and other	
18		relevant evidence	
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20	Generalisability	21 Discuss the generalisability (external validity) of the study results	12
21			
22	Other information		
23	Funding	22 Give the source of funding and the role of the funders for the present study	13
24		and, if applicable, for the original study on which the present article is	
25		based	
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.