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

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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).

Conclusions: Our study indicates that vomiting in the first trimester was associated with PTB. Additionally, women with underweight and normal pre-pregnancy BMI that experienced vomiting are more likely to have a PTB.

Keywords: vomiting; preterm birth; pre-pregnancy body mass index

Strengths and limitations of this study

1. The present study is a cohort study enrolled a large population of 317,463 pregnant women.

2. This is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women by pre-pregnancy BMI status.

3. Vomiting symptoms was based on self-reported, which may be a possible source of bias.

4. The prevalence of overweight and obesity were relatively low in our sample, and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

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

conducted in a University obstetric unit in Hong Kong revealed that the prevalence of NVP was 90.9% among 396 women.[13]

In previous studies, NVP was not found to be associated with primary maternal diseases such as gastrointestinal infections or allergies.[8] Recently there was a resurgence of interest in topics related to NVP, such as death,[14] pregnancy complications,[15] and birth outcomes.[16] Some studies reported that women with NVP were more likely to have a preterm birth (PTB) compared with symptom- free women.[15 17 18] Still, other studies have found no association between this phenomenon.[6 19] However, Czeizel and Puho have suggested that women with NVP had a lower risk of PTB.[20] A Norway prospective cohort study involving 51,675 pregnant women found nausea to decrease the risk for PTB by 14% but did not find NVP associated with PTB.[9]

To our knowledge, there has been only one case-control study, which was conducted in Chinese pregnant women that addressed the relationship between PTB and a severe form of NVP called *Hyperemesis Gravidarum*.[19] Information about the association between vomiting in the first trimester and risk of PTB in China is unclear. Furthermore, there has not been a study in which the population was grouped according to pre-pregnancy BMI to determine its contribution to the identification of the association between NVP and risk of PTB. Thus, our objective in the present study is to explore the association between vomiting in the first trimester and PTB as well as assess whether pre-pregnancy BMI modifies this association using a birth cohort study in Wuhan, China.

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

categorized into 3 groups: younger than 25, 25～34 years old, and 35 years old and older. A proxy for socioeconomic status was the maternal education which was categorized into 3 groups: less than high school, high school, and college. By parity, women were dichotomized into nullipara and multipara. Regarding gravidity, it was divided into less than 3 times and 3 times and more. Pre-pregnancy BMI was calculated as weight/height^2 and grouped into 4 categories according to Chinese standard of weight for adults.[22]

The main outcome variable was PTB. PTB was defined as gestational age <37 gestational weeks.[23] 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.

Statistical analysis

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

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.

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	**<0.001**
Male	6701	4.54	140903	95.46	
Parity					
Nullipara	11948	4.65	245121	95.35	**<0.001**
Multipara	3941	9.53	56453	93.47	
Gravidity					
<3	11471	4.59	238259	95.41	**<0.001**
⩾3	4418	6.52	63315	93.48	
Pre-pregnancy BMI(kg/m^2)					
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(⩾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)	*P*	Adjusted RR (95% CI)*	*P*
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

longer exposure times to chronic pathologies and unhealthy lifestyles,[30] and higher prevalence of maternal obesity in older mothers, which were associated with risks factors for PTB.[31] Several studies demonstrated that the lower the socio-economic and education level, the higher the probability of developing infection, and that was clearly associated with PTB before 30 weeks of gestation.[32 33]

In this large cohort study conducted among Chinese women, we have found an association between vomiting in the first trimester and PTB before 37 weeks of gestation. When compared with non-vomiting pregnant women, women that experienced vomiting were at an increased risk of PTB. Our results were inconsistent with that of other studies.[15 18 34 35] For example, Andrew and Puho indicated that there was a significant association of vomiting with a decreased risk of PTB,[20] and Naumann et al. found that vomiting was not associated with PTB.[27] The differences found among these studies may be attributed to race, definition or classification of vomiting, and the differential sample sizes of the populations mentioned above.

The possible causal link between vomiting and PTB remains elusive. The most common hypothesis proffered to explain the harmful effects of vomiting is based on the fact that vomiting leads to abnormal digestive function, which results in a lower nutrient intake of pregnant women.[14 36] Vomiting may also affect maternal and fetal physiology through dehydration and the modulation of stress-related risk factors.[37 38] Moreover, vomiting may cause low maternal weight gain during pregnancy, which has been associated with PTB as reported by Canadian research.[6]

Additionally, our results reveal that vomiting was a risk factor for PTB in women

with underweight and normal pre-pregnancy BMI, but not in overweight and obese women. Previous studies have estimated the risk factors for vomiting and PTB separately and found different effects of pre-pregnancy BMI on vomiting and PTB.[39-41] No study has assessed the association between vomiting and PTB by pre-pregnancy BMI. The biological mechanisms underlying the associations with maternal pre-pregnancy BMIs remain unclear. Gary et al. indicated that the relationship between pre-pregnancy BMI and risk of PTB were complex.[23] Although it was not statistically significant, a trend towards lower risk for PTB in obese women with vomiting was observed. We speculate that vomiting may have relatively few impacts on the nutrition of obese women due to their increased capacity for energy storage.

Strengths of this study are as follows. First, this is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women while assessing the association between PTB and vomiting by pre-pregnancy BMI status. Second, the data were collected from the large population-based cohort and linked to the WMCHMIS, providing thorough and detailed access to pregnancy and birth outcomes. Third, with such a large cohort size, many significant associations tend to appear, and the merit of these in the clinical setting is notable. However, there are two limitations. One is the reliance on self-reported data on vomiting. Retrospective evaluation of vomiting symptoms has been reported as a possible source of bias.[42] The other is that the prevalence of overweight and obesity were relatively low in our sample (6.17% and 1.10%, respectively) and the relationship between vomiting and

PTB in women with a high pre-pregnancy BMI needs to be further assessed.

Conclusion

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

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Ethics approval

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

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Patient consent

Obtained.

Competing interests

None declared.

Data sharing statement

No additional data are available.

Contribution to authorship

RHH, YWC, BZ designed the research; YWC, YMZ, MZL analyzed data; RHH, YWC, YL drafted the manuscript; ZMQ, MGV, SQX, TZZ, BZ revised the manuscript.

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Figure legends

Figure 1. Flow chart of population selection

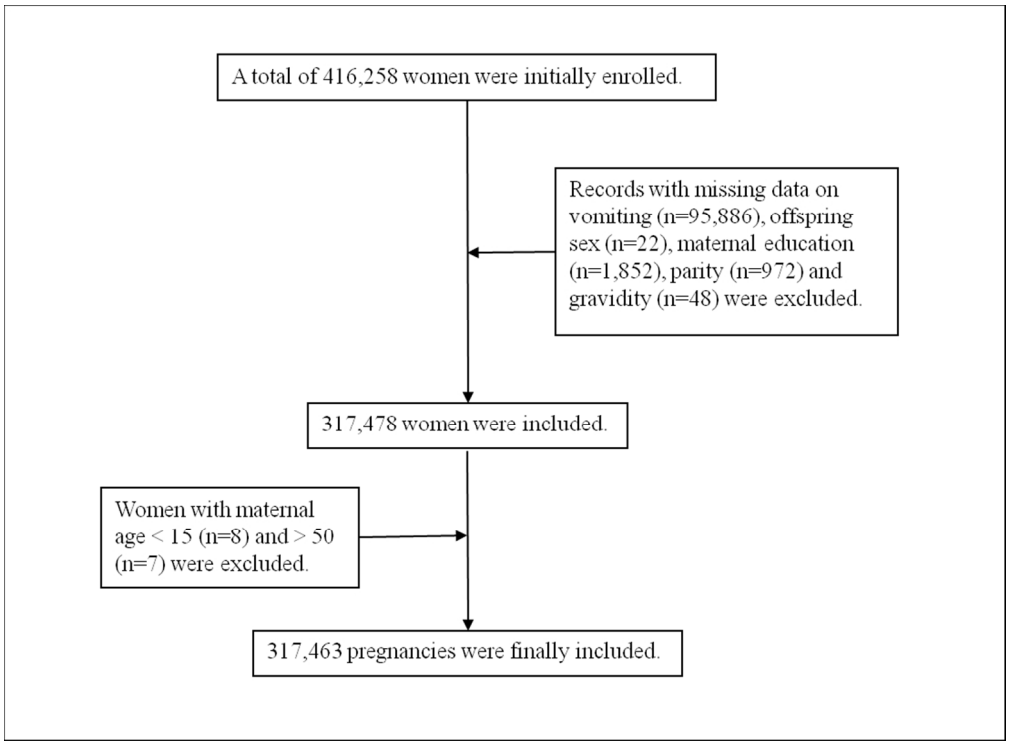

Figure 1 Flow chart of population selection

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.

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

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

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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 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).

Conclusions: Our study indicates that vomiting in the first trimester was associated with PTB. Additionally, women with underweight and normal pre-pregnancy BMI that experienced vomiting are more likely to have a PTB.

Keywords: vomiting; preterm birth; pre-pregnancy body mass index

Strengths and limitations of this study

1. The present study is a cohort study enrolled a large population of 317,463 pregnant women.

2. This is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women by pre-pregnancy BMI status.

3. Vomiting symptoms was based on self-reported, which may be a possible source of bias.

4. The prevalence of overweight and obesity were relatively low in our sample, and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

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

conducted in a University obstetric unit in Hong Kong revealed that the prevalence of NVP was 90.9% among 396 women.[13]

In previous studies, NVP was not found to be associated with primary maternal diseases such as gastrointestinal infections or allergies.[8] Recently there was a resurgence of interest in topics related to NVP, such as death,[14] pregnancy complications,[15] and birth outcomes.[16] Some studies reported that women with NVP were more likely to have a preterm birth (PTB) compared with symptom- free women.[15 17 18] Still, other studies have found no association between this phenomenon.[6 19] However, Czeizel and Puho have suggested that women with NVP had a lower risk of PTB.[20] A Norway prospective cohort study involving 51,675 pregnant women found nausea to decrease the risk for PTB by 14% but did not find NVP associated with PTB.[9]

To our knowledge, there has been only one case-control study, which was conducted in Chinese pregnant women that addressed the relationship between PTB and a severe form of NVP called *Hyperemesis Gravidarum*.[19] Information about the association between vomiting in the first trimester and risk of PTB in China is unclear. Furthermore, there has not been a study in which the population was grouped according to pre-pregnancy BMI to determine its contribution to the identification of the association between NVP and risk of PTB. Thus, our objective in the present study is to explore the association between vomiting in the first trimester and PTB as well as assess whether pre-pregnancy BMI modifies this association using a birth cohort study in Wuhan, China.

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

categorized into 3 groups: younger than 25, 25～34 years old, and 35 years old and older. A proxy for socioeconomic status was the maternal education which was categorized into 3 groups: less than high school, high school, and college. By parity, women were dichotomized into nullipara and multipara. Regarding gravidity, it was divided into less than 3 times and 3 times and more. Pre-pregnancy BMI was calculated as weight/height^2 and grouped into 4 categories according to Chinese standard of weight for adults.[22]

The main outcome variable was PTB. PTB was defined as gestational age <37 gestational weeks.[23] 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.

Statistical analysis

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

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.

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					
Male	9188	5.41	160671	94.59	**<0.001**
Female	6701	4.54	140903	95.46	
Parity					
Nullipara	11948	4.65	245121	95.35	**<0.001**
Multipara	3941	6.53	56453	93.47	
Gravidity					
<3	11471	4.59	238259	95.41	**<0.001**
⩾3	4418	6.52	63315	93.48	
Pre-pregnancy BMI(kg/m^2)					

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(⩾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)	*P*	Adjusted OR (95% CI)*	*P*
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	

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

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 longer exposure times to chronic pathologies and unhealthy lifestyles,[30] and higher prevalence of maternal obesity in older mothers, which were associated with risks factors for PTB.[31] Several studies demonstrated that the lower the socio-economic and education level, the higher the probability of developing infection, and that was clearly associated with PTB before 30 weeks of gestation.[32 33]

In this large cohort study conducted among Chinese women, we have found an association between vomiting in the first trimester and PTB before 37 weeks of gestation. When compared with non-vomiting pregnant women, women that experienced vomiting were at an increased risk of PTB. Our results were inconsistent with that of other studies.[15 18 34 35] For example, Andrew and Puho indicated that there was a significant association of vomiting with a decreased risk of PTB,[20] and Naumann et al. found that vomiting was not associated with PTB.[27] The differences found among these studies may be attributed to race, definition or classification of vomiting, and the differential sample sizes of the populations mentioned above.

The possible causal link between vomiting and PTB remains elusive. The most common hypothesis proffered to explain the harmful effects of vomiting is based on

the fact that vomiting leads to abnormal digestive function, which results in a lower nutrient intake of pregnant women.[14 36] Vomiting may also affect maternal and fetal physiology through dehydration and the modulation of stress-related risk factors.[37 38] Moreover, vomiting may cause low maternal weight gain during pregnancy, which has been associated with PTB as reported by Canadian research.[6]

Additionally, our results reveal that vomiting was a risk factor for PTB in women with underweight and normal pre-pregnancy BMI, but not in overweight and obese women. Previous studies have estimated the risk factors for vomiting and PTB separately and found different effects of pre-pregnancy BMI on vomiting and PTB.[39-41] No study has assessed the association between vomiting and PTB by pre-pregnancy BMI. The biological mechanisms underlying the associations with maternal pre-pregnancy BMIs remain unclear. Gary et al. indicated that the relationship between pre-pregnancy BMI and risk of PTB were complex.[23] Although it was not statistically significant, a trend towards lower risk for PTB in obese women with vomiting was observed. We speculate that vomiting may have relatively few impacts on the nutrition of obese women due to their increased capacity for energy storage.

Strengths of this study are as follows. First, this is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women while assessing the association between PTB and vomiting by pre-pregnancy BMI status. Second, the data were collected from the large population-based cohort and linked to the WMCHMIS, providing thorough and detailed access to pregnancy and birth

outcomes. Third, with such a large cohort size, many significant associations tend to appear, and the merit of these in the clinical setting is notable. However, there are two limitations. One is the reliance on self-reported data on vomiting. Retrospective evaluation of vomiting symptoms has been reported as a possible source of bias.[42] The other is that the prevalence of overweight and obesity were relatively low in our sample (6.17% and 1.10%, respectively) and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

Conclusion

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

Acknowledgement

We are extremely grateful to all the families who took part in this study, the staff of the Wuhan Health Bureau, and all the hospitals and community health centers involved in this study.

Ethics approval

The Institutional Review Board of Wuhan Medical and Healthcare Center for Women

and Children received and approved this study (approved on 10/13/2016).

Funding

None.

Patient consent

Obtained.

Competing interests

None declared.

Data sharing statement

No additional data are available.

Contribution to authorship

RHH, YWC, BZ designed the research; YWC, YMZ, MZL analyzed data; RHH, YWC, YL drafted the manuscript; ZMQ, MGV, SQX, TZZ, BZ revised the manuscript.

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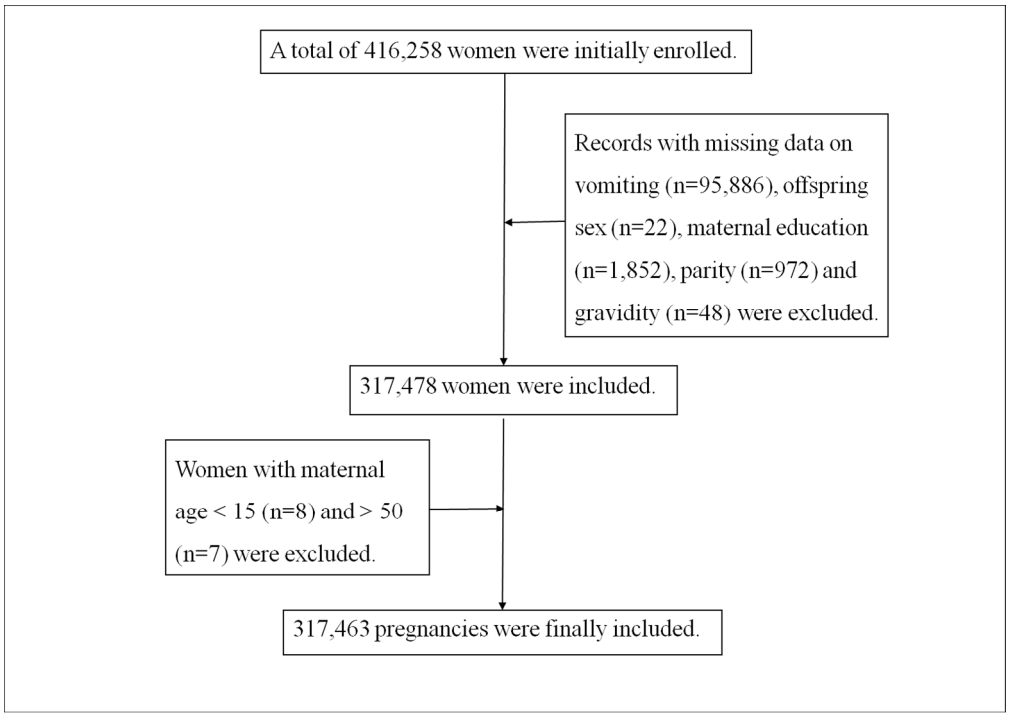
Figure legends

Figure 1. Flow chart of population selection



269x190mm (300 x 300 DPI)

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)	*P*	Adjusted OR (95% CI)*	*P**
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)	<0.001	1.00(Reference)	<0.001
Female	6701 (4.54)	140903 (95.46)	0.83(0.81,0.86)		0.84(0.82,0.87)	
Parity						
Nullipara	11948 (4.65)	245121 (95.35)	1.00(Reference)	<0.001	1.00(Reference)	<0.001
Multipara	3941 (6.55)	56453 (93.47)	1.4(1.38,1.49)		1.14(1.09,1.20)	

Gravidity						
<3	11471 (4.59)	238259 (95.41)	1.00(Reference)	<0.001	1.00(Reference)	<0.001
⩾3	4418 (6.52)	63315 (93.48)	1.45(1.40,1.50)		1.211(1.16,1.27)	
Pre-pregnancy						
BMI(kg/m^2)						
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)	<0.001	1.05(1.02, 1.09)	0.0048
No	10911 (4.90)	211695 (95.10)	1.00(Reference)		1.00(Reference)	

***** 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

		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.

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

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Epidemiology
Keywords:	vomiting, preterm birth, pre-pregnancy body mass index

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

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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 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).

Conclusions: Our study indicates that vomiting in the first trimester was associated with PTB. Additionally, women with underweight and normal pre-pregnancy BMI that experienced vomiting are more likely to have a PTB.

Keywords: vomiting; preterm birth; pre-pregnancy body mass index

Strengths and limitations of this study

1. The present study is a cohort study enrolled a large population of 317,463 pregnant women.

2. This is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women by pre-pregnancy BMI status.

3. Vomiting symptoms was based on self-reported, which may be a possible source of bias.

4. The prevalence of overweight and obesity were relatively low in our sample, and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

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

conducted in a University obstetric unit in Hong Kong revealed that the prevalence of NVP was 90.9% among 396 women.[13]

In previous studies, NVP was not found to be associated with primary maternal diseases such as gastrointestinal infections or allergies.[8] Recently there was a resurgence of interest in topics related to NVP, such as death,[14] pregnancy complications,[15] and birth outcomes.[16] Some studies reported that women with NVP were more likely to have a preterm birth (PTB) compared with symptom- free women.[15 17 18] Still, other studies have found no association between this phenomenon.[6 19] However, Czeizel and Puho have suggested that women with NVP had a lower risk of PTB.[20] A Norway prospective cohort study involving 51,675 pregnant women found nausea to decrease the risk for PTB by 14% but did not find NVP associated with PTB.[9]

To our knowledge, there has been only one case-control study, which was conducted in Chinese pregnant women that addressed the relationship between PTB and a severe form of NVP called *Hyperemesis Gravidarum*.[19] Information about the association between vomiting in the first trimester and risk of PTB in China is unclear. Furthermore, there has not been a study in which the population was grouped according to pre-pregnancy BMI to determine its contribution to the identification of the association between NVP and risk of PTB. Thus, our objective in the present study is to explore the association between vomiting in the first trimester and PTB as well as assess whether pre-pregnancy BMI modifies this association using a birth cohort study in Wuhan, China.

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

categorized into 3 groups: younger than 25, 25～34 years old, and 35 years old and older. A proxy for socioeconomic status was the maternal education which was categorized into 3 groups: less than high school, high school, and college. By parity, women were dichotomized into nullipara and multipara. Regarding gravidity, it was divided into less than 3 times and 3 times and more. Pre-pregnancy BMI was calculated as weight/height^2 and grouped into 4 categories according to Chinese standard of weight for adults.[22]

The main outcome variable was PTB. PTB was defined as gestational age <37 gestational weeks.[23] 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.

Statistical analysis

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

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.

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					
Male	9188	5.41	160671	94.59	**<0.001**
Female	6701	4.54	140903	95.46	
Parity					
Nullipara	11948	4.65	245121	95.35	**<0.001**
Multipara	3941	6.53	56453	93.47	
Gravidity					
<3	11471	4.59	238259	95.41	**<0.001**
⩾3	4418	6.52	63315	93.48	
Pre-pregnancy BMI(kg/m^2)					

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(⩾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)	*P*	Adjusted OR (95% CI)*	*P*
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]

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

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 longer exposure times to chronic pathologies and unhealthy lifestyles,[30] and higher prevalence of maternal obesity in older mothers, which were associated with risks factors for PTB.[31] Several studies demonstrated that the lower the socio-economic and education level, the higher the probability of developing infection, and that was clearly associated with PTB before 30 weeks of gestation.[32 33]

In this large cohort study conducted among Chinese women, we have found an association between vomiting in the first trimester and PTB before 37 weeks of gestation. When compared with non-vomiting pregnant women, women that experienced vomiting were at an increased risk of PTB. Our results were inconsistent with that of other studies.[15 18 34 35] For example, Andrew and Puho indicated that there was a significant association of vomiting with a decreased risk of PTB,[20] and Naumann et al. found that vomiting was not associated with PTB.[27] The differences found among these studies may be attributed to race, definition or classification of vomiting, and the differential sample sizes of the populations mentioned above.

The possible causal link between vomiting and PTB remains elusive. The most common hypothesis proffered to explain the harmful effects of vomiting is based on

the fact that vomiting leads to abnormal digestive function, which results in a lower nutrient intake of pregnant women.[14 36] Vomiting may also affect maternal and fetal physiology through dehydration and the modulation of stress-related risk factors.[37 38] Moreover, vomiting may cause low maternal weight gain during pregnancy, which has been associated with PTB as reported by Canadian research.[6]

Additionally, our results reveal that vomiting was a risk factor for PTB in women with underweight and normal pre-pregnancy BMI, but not in overweight and obese women. Previous studies have estimated the risk factors for vomiting and PTB separately and found different effects of pre-pregnancy BMI on vomiting and PTB.[39-41] No study has assessed the association between vomiting and PTB by pre-pregnancy BMI. The biological mechanisms underlying the associations with maternal pre-pregnancy BMIs remain unclear. Gary et al. indicated that the relationship between pre-pregnancy BMI and risk of PTB were complex.[23] Although it was not statistically significant, a trend towards lower risk for PTB in obese women with vomiting was observed. We speculate that vomiting may have relatively few impacts on the nutrition of obese women due to their increased capacity for energy storage.

Strengths of this study are as follows. First, this is the first study exploring the relationship between vomiting in the first trimester and PTB in Chinese women while assessing the association between PTB and vomiting by pre-pregnancy BMI status. Second, the data were collected from the large population-based cohort and linked to the WMCHMIS, providing thorough and detailed access to pregnancy and birth

outcomes. Third, with such a large cohort size, many significant associations tend to appear, and the merit of these in the clinical setting is notable. However, there are two limitations. One is the reliance on self-reported data on vomiting. Retrospective evaluation of vomiting symptoms has been reported as a possible source of bias.[42] The other is that the prevalence of overweight and obesity were relatively low in our sample (6.17% and 1.10%, respectively) and the relationship between vomiting and PTB in women with a high pre-pregnancy BMI needs to be further assessed.

Conclusion

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

Acknowledgement

We are extremely grateful to all the families who took part in this study, the staff of the Wuhan Health Bureau, and all the hospitals and community health centers involved in this study.

Ethics approval

The Institutional Review Board of Wuhan Medical and Healthcare Center for Women

and Children received and approved this study (approved on 10/13/2016).

Funding

None.

Patient consent

Obtained.

Competing interests

None declared.

Data sharing statement

No additional data are available.

Contribution to authorship

RHH, YWC, BZ designed the research; YWC, YMZ, MZL analyzed data; RHH, YWC, YL drafted the manuscript; ZMQ, MGV, SQX, TZZ, BZ revised the manuscript.

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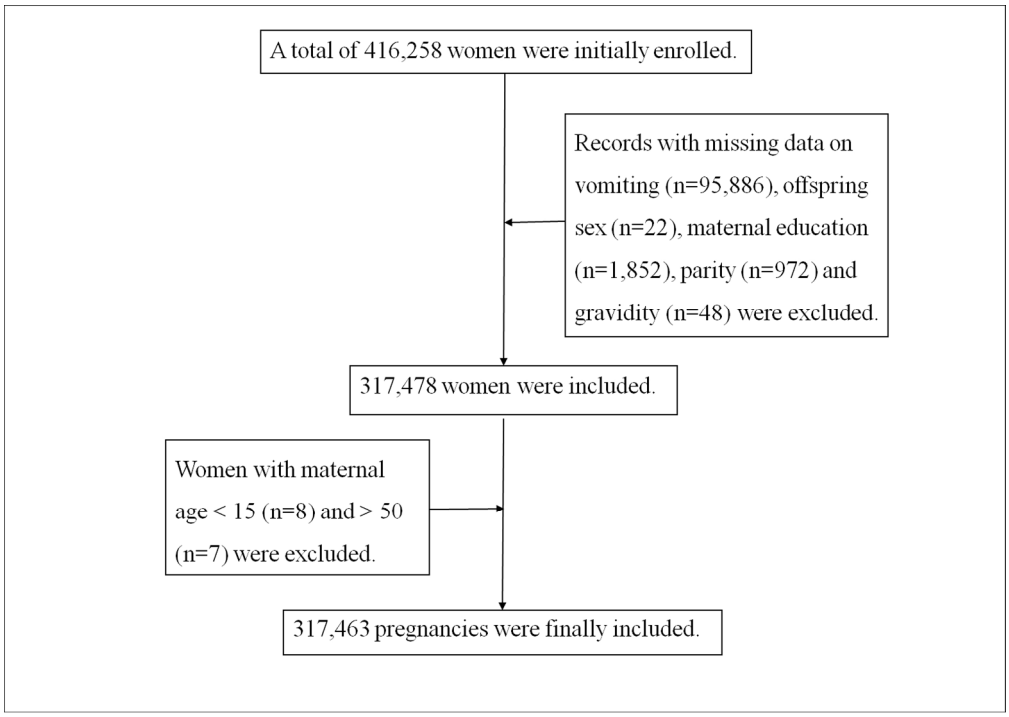
Figure legends

Figure 1. Flow chart of population selection



269x190mm (300 x 300 DPI)

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)	*P*	Adjusted OR (95% CI)*	*P**
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)	<0.001	1.00(Reference)	<0.001
Female	6701 (4.54)	140903 (95.46)	0.83(0.81,0.86)		0.84(0.82,0.87)	
Parity						
Nullipara	11948 (4.65)	245121 (95.35)	1.00(Reference)	<0.001	1.00(Reference)	<0.001
Multipara	3941 (6.55)	56453 (93.47)	1.4(1.38,1.49)		1.14(1.09,1.20)	

Gravidity						
<3	11471 (4.59)	238259 (95.41)	1.00(Reference)	<0.001	1.00(Reference)	<0.001
⩾3	4418 (6.52)	63315 (93.48)	1.45(1.40,1.50)		1.211(1.16,1.27)	
Pre-pregnancy						
BMI(kg/m^2)						
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)	<0.001	1.05(1.02, 1.09)	0.0048
No	10911 (4.90)	211695 (95.10)	1.00(Reference)		1.00(Reference)	

***** 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

		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.