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# Nausea and Vomiting in Early Pregnancy and the Risk of Neural Tube Defects: a Case-Control Study

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There has been considerable professional debate on the association between nausea and vomiting in early pregnancy (NVP) and neural tube defects (NTDs) risk. This study explored the association between NVP and NTDs risk, and the effect of folic acid supplements on the association. A 1 : 1 matched case-control study was conducted and conditional logistic regression model was used to analyze the associations. The result showed the odds ratio (OR) of severe NVP for NTDs was 2.403 (95%CI 1.437,4.017;  $P < 0.001$ ) and that of moderate NVP was 1.469 (95%CI 1.063,2.031;  $P = 0.020$ ) compared with light NVP when adjusted by the potential confounders. Stratified by intake of folic acid supplements, the ORs for severe and moderate NVP turned to 2.147 (95%CI 1.140, 4.043;  $P = 0.018$ ) and 2.055 (95%CI 1.320, 3.199;  $P = 0.001$ ) in the stratum of non-intake of folic acid supplements while ORs reduced to 1.851 (95%CI 0.729, 4.699;  $P = 0.195$ ) and 1.003 (95%CI 0.594, 1.694;  $P = 0.992$ ) in the stratum of intake of folic acid supplements, respectively. We conclude that severe/moderate NVP has an association with the risk of NTDs, which was not found in the group with intake of folic acid supplements. Folic acid supplements should be recommended to use for the prevention of NTDs.

Neural tube defects (NTDs) are one group of severe defects in the central nervous system, always leading to infant deaths or disabilities. Data from the National Center for Birth Defects Monitor of China showed that the incidence rate of NTDs was 4.50 per ten thousand in the year of 2011. Lots of environmental and genetic factors have been proved to be risk factor of NTDs, such as smoking, passive smoking, obesity, lack of folic acid, methylenetetrahydrofolate reductase C677T mutation and so on<sup>1-12</sup>. Yet, there has been less professional debate on the association between nausea and vomiting in early pregnancy (NVP) and the risk of NTDs.

NVP is a common experience in pregnancy and the meta-analytic average rate was 69.4%, but reported rates vary widely<sup>13</sup>. Meanwhile, NVP is found more often in Western countries and urban populations and rarely among Africans, Native Americans, Eskimos, and most Asian populations<sup>14</sup>. Although most women with NVP have symptoms limited to the first trimester from six weeks to 12 weeks, a small proportion of women have a prolonged course with symptoms extending until delivery. Women with severe NVP may suffer from hyperemesis gravidarum, an entity distinct from NVP, which may lead to maternal and fetal morbidity if left untreated.

Most studies have demonstrated that NVP is associated with a favorable outcome of the fetus. Weigel et al. found a strong significant association between NVP and decreased risk of miscarriage, but no consistent associations with perinatal mortality<sup>15</sup>. However, an increased risk of intrauterine growth retardation and low birth weight was associated with the women with severe NVP<sup>16,17</sup>. Previous studies also showed no difference in congenital abnormalities between those with and without NVP<sup>11</sup> and a lower risk of congenital heart defects in infants born to women with early onset of NVP requiring antiemetic use compared to women without nausea<sup>18</sup>.

However, there has been considerable professional debate on the association between NVP and the risk of NTDs. Czeizel et al. suggested an inverse association between severe NVP and the risk of some congenital abnormalities, including NTDs<sup>19</sup>. While this association was not observed in other studies<sup>20,21</sup>. NVP may reduce energy intake and levels of anabolic hormones, insulin, and insulin growth factor leading to a shunting of scarce nutrients to the placenta and fetus<sup>22</sup>, also including maternal level of folic acid. The evidence of public health suggests that daily folic acid supplements have a significant protective effect in preventing NTDs. It remains unknown whether the folic acid supplements intake would affect the association between NVP and NTDs.



Table 1 | Characteristics of the subject women in the case and control groups

Characteristics	Case group		Control group		OR (95%CI)	P
	Number	%	Number	% (%)		
Age (years)						
≤24	75	16.3	90	19.6	1.000	
24~28	161	35.1	176	38.3	1.109(0.752,1.636)	0.603
>28	223	48.6	193	42.1	1.397(0.964,2.027)	0.078
Occupation						
Manual work	406	88.5	364	79.3	2.355(1.547,3.585)	<0.001
Brain work	53	11.6	95	20.7	1.000	
Education level						
≤Middle school	417	90.9	358	78.0	3.034(1.994,4.617)	<0.001
>Middle school	42	9.2	101	22.0	1.000	
Annual income (RMB)						
Low (≤12000)	299	65.1	189	41.2	3.245(2.356,4.47)	<0.001
High (>12000)	160	34.9	270	58.8	1.000	
BMI*(kg/m <sup>2</sup> )						
≤24	340	74.1	370	80.6	1.000	
>24	119	25.9	89	19.4	1.484(1.075,2.048)	0.016
Passive smoking						
Yes	177	38.6	78	17.0	3.750(2.596,5.416)	<0.001
No	282	61.4	381	83.0	1.000	
Exposure to pesticide						
Yes	32	7.0	6	1.3	6.196(2.41,15.93)	<0.001
No	427	93.0	453	98.7	1.000	
Intake of folic acid supplements						
Yes	142	30.9	230	50.1	0.429(0.321,0.572)	<0.001
No	317	69.1	229	49.9	1.000	
Maternal chronic diseases						
Yes	30	6.5	14	3.1	2.332(1.186,4.586)	0.014
No	429	93.5	445	96.9	1.000	

Meanwhile, the severity of nausea and vomiting was associated with the frequency of feelings of depression and adverse effects on women's relationships, which may have an effect on the risk of NTDs<sup>23</sup>.

Therefore, we conducted a matched case-control study in China to further explore the association between NVP and NTDs risk, and the effect of folic acid supplements on the association between NVP and NTDs risk.

## Methods

The 1:1 matched case-control study was conducted in Shanxi Province and Shandong Province of China. We identified study subjects and collected the information from the registration cards and hospital records through the National Center for Birth Defects Monitor of China, the Maternal and Child Care Service Centers, the Family Planning Centers and the local hospitals. We excluded those without detailed home address and contact information.

Cases were the women with any infant or fetus with a diagnosis (ICD-10) of anencephaly (Q00.0), spina bifida (Q05), or encephalocele (Q01) at birth or prenatally within 2 years before the survey date (from March to December 2008). Controls were the women with live born infants, randomly selected without an apparent congenital malformation. The matching criteria were that the matched case and control were from the same region, the same hospital and childbirth in the same year in order to control the potential confounding factors by the above factors and reduce the sample size.

In the study, structured questionnaires were used for data collection. The questionnaire contained questions on maternal socio-demographic characteristics (age, education, occupation, and annual income), conditions of fetuses or infants, height and prepregnancy weight, exposure to passive smoking and pesticide, chronic diseases (anemia, diabetes, epilepsy, hyperthyroidism, tumor and hypertension), fever or cold, NVP status, intake of folic acid supplements and nutritional status in the periconceptional period. The questionnaires were administered through household-to-household survey by well-trained interviewers who had no knowledge of the main hypotheses of the study. The study protocol was reviewed and approved by the Ethics Review Committee of Public Health at Shandong University. The methods were carried out in accordance with the approved guidelines. Informed consent forms were shown to the subjects and their spouses, and signed by the subjects with the assistance of community/village doctors.

Severity of NTD was categorized by three stages: light NVP means one or none of most situation in early pregnancy with salivation or mild nausea and vomiting in early

morning, which would not affect daily life; moderate NVP means that the symptoms of nausea and vomiting aggravate and occur to be not limited to the morning, which can be released after an adequate rest; severe NVP means the continuous symptoms of nausea and vomiting occur and the women need to rest in bed or be hospitalized.

Descriptive statistics were calculated for all variables; continuous variables were summarized as means and standard deviations or median and range, and categorical variables were summarized as frequencies and proportions. To determine the difference between groups, independent t test, chi-square test, or Fisher exact was used where appropriate. Body mass index (BMI) was calculated by prepregnancy weight (kg) divided by the square of height (m). Differences of categorical data between the case women and the control women were examined by conditional logistic regression models which were used to calculate odds ratios (ORs) and their 95% confidence intervals (CIs). Conditional logistic regression model was used in order to analyze the association between NVP and NTDs stratified by the variable of intake of folic acid supplements. Adjusted ORs and their 95% CIs were calculated by adjusting for the potential confounders. A two-sided P value of less than 0.05 was considered to be statistically significant. All analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA).

## Results

Totally 459 case women and 459 control women were recruited in the study. There were 194 anencephaly, 200 spina bifida and 65 encephalocele in the case group. The characteristics of the women in the case and control groups were presented in Table 1. The differences between the case and the control groups were statistically significant for occupation, education level, annual income, BMI, passive smoking, exposure to pesticide, intake of folic acid supplements and maternal chronic diseases (all  $P < 0.05$ ) except for age.

NVP distribution in case and control groups and the OR values between NVP and NTDs risk stratified by the variable of intake of folic acid supplements were shown in Table 2. In the case women, 11.5% (53/459) had severe NVP and 29.0% (133/459) had moderate NVP in the first trimester. In the control women, 6.1% (28/459) had severe NVP and 24.6% (113/459) had moderate NVP in the first trimester. The OR of NTDs for the women with severe NVP was 2.403 (95%CI 1.437,4.017;  $P < 0.001$ ) and that with moderate NVP was 1.469 (95%CI 1.063,2.031;  $P = 0.020$ ), compared to the women


**Table 2 | NVP distribution in case and control groups and the OR values between NVP and NTDs stratified by intake of folic acid supplements**

Factor	Case	Control	P	Crude		Adjusted*	
	n=459	n=459		OR (95%CI)	P	OR (95%CI)	P
NVP#							
Light	273	318	0.002	1.000		1.000	
Moderate	133	113		1.469(1.063,2.031)	0.020	1.626(1.117,2.366)	0.011
Severe	53	28		2.403(1.437,4.017)	<0.001	1.966(1.098,3.523)	0.023
Intake of folic acid supplements#							
Light NVP	97	155	0.566	1.000		1.000	
Moderate NVP	35	64		1.003(0.594,1.694)	0.992	0.967(0.537,1.744)	0.912
Severe NVP	10	11		1.851(0.729,4.699)	0.195	1.920(0.710,5.197)	0.199
Non-intake of folic acid supplements#							
Light NVP	176	163	<0.001	1.000		1.000	
Moderate NVP	98	49		2.055(1.320,3.199)	0.001	2.292(1.408,3.730)	0.001
Severe NVP	43	17		2.147(1.140,4.043)	0.018	2.103(1.058,4.180)	0.034

\*: Adjusted OR and 95%CI were calculated by adjusting for the potential confounders, including age, occupation, education, annual income, BMI, passive smoking, exposure to pesticide, chronic disease, use of folic acid supplements.  
#: The conditional logistic regression model was used to calculate the parameters.

with light NVP when adjusted by the potential confounders. The interaction between NVP and intake of folic acid supplements demonstrated a significantly antagonistic effect ( $P=0.034$ ). Interestingly, when stratified by intake of folic acid supplements, the ORs for severe and moderate NVP turned to 2.147 (95%CI 1.140, 4.043;  $P=0.018$ ) and 2.055 (95%CI 1.320, 3.199;  $P=0.001$ ) compared to light NVP in the stratum of non-intake of folic acid supplements, respectively. While in the stratum of intake of folic acid supplements, the ORs for severe and moderate NVP reduced to 1.851 (95%CI 0.729, 4.699) and 1.003 (95%CI 0.594, 1.694), respectively, which demonstrated no statistically significant differences compared with light NVP ( $P=0.195$  and  $P=0.992$ ).

The distribution and risk of NVP for the different subtypes of NTDs were shown in Table 3 and Table 4. The risk of anencephaly was significantly associated with severe NVP and the OR value was 3.738 (95%CI 1.158, 12.073;  $P=0.028$ ) when adjusted by the potential confounders. However, no statistically significant associations were found between NVP and spina bifida/encephalocele (all  $P>0.05$ ). When stratified by intake of folic acid supplements, the risk of severe and moderate NVP for anencephaly rose in the group of non-intake of folic acid supplements and reduced to no statistically significant differences in the group of intake of folic acid supplements. For spina bifida, it showed no differences stratified by intake of folic acid supplements.

## Discussion

This study had explored the association between NVP and NTDs risk. The results showed that severe or moderate NVP had a significant association with the risk of NTDs. While this association was not found in the group with the intake of folic acid supplements.

The etiology of NVP has been well understood, but it is widely believed that physiological, psychological, genetic, and cultural components are contributing factors<sup>14,18</sup>. The occurrence of NVP may be of benefit in pregnancy and less likely to result in miscarriage, pre-term delivery, or intrauterine growth retardation. The Maternal and Embryo Protection Hypothesis posits that pregnancy sickness results in adaptive dietary changes that reduce the exposure of the fetus and mother to dietary pathogens, toxins and parasites by reducing the intake of foods such as meat, fish and dairy products<sup>24</sup>. But the study by Weigel et al. was little direct evidence for this hypothesis<sup>25</sup>. Studies suggested that NVP was promoted by secretion of human chorionic gonadotrophin (hCG), largely on the basis of the coincidence between the onset of NVP and hCG secretion and the peaks of both at around 12 to 14 weeks in the first trimester<sup>26–28</sup>. Abnormal concentrations of hCG are associated with poor pregnancy outcomes. It seems that NVP and hCG are related and nutrient restriction during critical periods of embryonic development may ensure production of hCG at optimal levels to protect placental development and optimize nutrient partitioning between maternal and fetal tissues.

**Table 3 | The distribution NVP in the case and control groups for different subtypes of NTDs**

Factor	Anencephaly			Spina bifida			Encephalocele		
	Case	Control	P	Case	Control	P	Case	Control	P
NVP									
Light	114	135	0.013	121	136	0.294	38	47	0.064*
Moderate	58	51		57	46		18	16	
Severe	22	8		22	18		9	2	
Intake of folic acid supplements#									
Light NVP	38	65	0.590	43	66	0.742	16	24	0.625*
Moderate NVP	13	33		16	22		6	9	
Severe NVP	2	4		7	7		1	0	
Non-intake of folic acid supplements#									
Light NVP	76	70	0.002	78	70	0.367	22	23	0.170*
Moderate NVP	45	18		41	24		12	7	
Severe NVP	2	4		15	11		8	2	

\*: The P value was calculated by Fisher exact test.



Table 4 | Adjusted OR values between NVP and different subtypes of NTDs stratified by intake of folic acid supplements

Factor	Anencephaly		Spina bifida		Encephalocele	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
NVP <sup>#</sup>						
Light	1.000		1.000		1.000	
Moderate	1.744(0.951,3.199)	0.072	1.561(0.898,2.711)	0.114	2.438(0.666,8.922)	0.093
Severe	3.738(1.158,12.073)	0.028	1.313(0.615,2.805)	0.482	6.087(0.741,50.035)	0.197
Intake of folic acid supplements <sup>#</sup>						
Light NVP	1.000		1.000		1.000	
Moderate NVP	0.842(0.330,2.146)	0.718	1.099(0.438,2.760)	0.841	0.762(0.092,6.375)	0.998
Severe NVP	1.182(0.149,9.356)	0.874	1.941(0.558,6.744)	0.297	-	-
Non-intake of folic acid supplements <sup>#</sup>						
Light NVP	1.000		1.000		1.000	
Moderate NVP	3.148(1.340,7.398)	0.009	2.003(0.971,4.129)	0.060	3.824(0.761,19.222)	0.104
Severe NVP	6.724(1.519,29.758)	0.012	1.137(0.447,2.896)	0.787	5.606(0.443,70.882)	0.183

\*: Adjusted OR and 95%CI were calculated by adjusting the potential confounders, including age, occupation, education, annual income, BMI, passive smoking, exposure to pesticide, chronic disease, and intake of folic acid supplements.

#: The conditional logistic regression model was used to calculate the parameters.

In our study, we found an opposite effect: a higher level of pregnancy sickness was correlated with a worse pregnancy outcome- a higher likelihood of neural tube defects. The advocates of the maternal and embryo protection hypothesis have not considered the potential costs of pregnancy sickness, in particular, reduced dietary intake. Lee et al. reported that morning sickness in pregnant women result in poor dietary diversity and reduced intakes of energy, protein, and micronutrients and, consequently, adversely affected infant outcome as well as maternal weight gain during early pregnancy<sup>29</sup>. In that case, reduced dietary intake certainly will influence or decrease the level of folic acid, which is mainly depending on food intake. It has been proved that folate deficiency could increase the risk of NTDs while intake of folic acid supplements could decrease the risk of NTDs<sup>11</sup>, which is also observed from our study. The result demonstrated that severe NVP was related to the risk of NTDs in this study. Stratified by the intake of folic acid supplements, the risk of NTD by severe NVP was decreased in the group with intake of folic acid supplements. The assumption is partly proved that severe NVP may reduce the intake of nutrition and then lower the level of folic acid in the maternal body, leading to the increased risk of NTDs. These results were different from those by Czeizel et al<sup>30</sup>. The effect of NVP on NTDs risk may depend on the level of hCG and folic acid. Of course, drug treatment on NVP was not considered as a limitation in this study.

In the study, the risk of anencephaly was associated with severe NVP, while spina bifida and encephalocele were not. The NVP may have different effects on the risk of anencephaly and the other two subtypes, which means, the hypothesis was further supported that anencephaly had a different pathogenic mechanism from the other two subtypes. Anencephaly may be more sensitive than spina bifida and encephalocele to folate deficiency. Folic acid supplements are likely to improve the status of folate level in the maternal body changed by NVP.

Although some confounders have been adjusted, considering other potential confounders, both NVP and NTDs might be the results of some underlying conditions. The association between NVP and NTDs needs further study considering more potential risk factors. The results showed a strong effect of severe NVP on the risk of encephalocele. However, the actual frequency in both of the case and control women used for calculation was too small to be convincing. Further studies are needed to clarify the actual relationship between severe NVP and the risk of encephalocele.

In conclusion, this case-control study reveals that severe or moderate NVP has an association with the risk of NTDs, which was not

found in the group with intake of folic acid supplements. So folic acid supplements should be recommended within three months before pregnancy or in the first trimester to use for prevention of NTDs.

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## Author contributions

Conceived and designed the experiments: Z.T.Z. Performed the experiments: Q.B.L. Z.P.W. L.J.G. M.W. X.H.S. R.G. Analyzed the data: Q.B.L. Z.P.W. Z.T.Z. Contributed reagents/materials/analysis tools: Q.B.L. Z.P.W. L.J.G. X.H.S. R.G. M.W. Wrote the paper: Q.B.L. Z.P.W. Z.T.Z.

## Additional information

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