Passive Smoking During the Periconceptional Period and Risk for Neural Tube Defects in Offspring — Five Counties, Shanxi Province, China, 2010–2016

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Summary

What is already known about this topic?
Passive smoking during pregnancy, which is prevalent in China, has been reported to be associated with an increased risk for neural tube defects (NTDs) in five counties of Shanxi Province in northern China.

What is added by this report?
After 4 years since the implementation of the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) in China, 59.4% of mothers of NTDs cases and 29.4% of mothers of healthy controls reported passive smoking during the periconceptional period. The association between periconceptional passive smoking and an increased risk for NTDs remains in the study population.

What are the implications for public health practice?
It’s urgent to take measures to prevent passive smoking among pregnant women to minimize the harmful effects on offspring.

Neural tube defects (NTDs) are severe congenital malformations in the central nervous system, which include anencephaly, spina bifida, and encephalocele. Research has confirmed that folic acid supplementation during the periconceptional period has a protective effect (1–2). Nonetheless, some NTDs are not preventable by folic acid supplementation. Periconceptional exposure to passive smoking has been reported to increase the risk of NTDs (3–4). The adverse effects of maternal passive smoking as a potential risk factor for NTDs is getting more attention (5). China is the largest producer and consumer of tobacco products in the world, with more than 300 million smokers and 740 million nonsmokers exposed to second-hand smoke (6). Since the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) officially took effect in China in 2006, China has taken strong measures to ban smoking in public places. This study aimed to investigate the effect of maternal passive smoking exposure on the risk of NTDs in offspring in five counties within Shanxi Province of China after 4 years of FCTC implementation. The results showed that there was an association between periconceptional passive smoking and an increased risk for NTDs. Measures need to be taken to prevent passive smoking among pregnant women to minimize the harmful effects on offspring.

Data were analyzed from an ongoing case-control study based on population-based birth-defect surveillance system that covered five counties (Xiyang, Pingding, Taigu, Shouyang, and Zezhou) in Shanxi Province. The surveillance system monitors major external structural birth defects that were diagnosed prenatally or neonatally. When one case with any major external structural birth defect including NTDs was identified, one healthy newborn infant of the same sex in the same region and with the closest date of conception to the case was selected as the healthy control. Information was collected through in-person interviews by trained healthcare workers before discharge from the hospital within 10 days after delivery, using a structured questionnaire including demographics, gravidity history, lifestyle behaviors, maternal active smoking, and passive smoking. For the current study, we included the subjects investigated from 2010 to 2016. The study excluded 12 women (1.5%) who reported active smoking and 27 women (3.4%) whose active or passive smoking status were missing. This study defined passive smoking as exposure to secondhand smoke at least once per week and at least one cigarette each time on average in their environment (such as at home, in the workspace or other public places) from 1 month before to 2 months after pregnancy. The study was approved by the Institutional Review Board of Peking University. Written informed consent was provided by all participants.
Logistic regression was used to evaluate the association between maternal passive smoking and risk for NTDs by crude odds ratio (OR) including 95% confidence intervals (95% CIs) and adjusted OR including 95% CIs after adjusting for potential confounders. The confounding variables included maternal age, pre-pregnancy body mass index (BMI), education, fever or flu in early pregnancy, nausea and vomiting during pregnancy (NVP), periconceptional folic acid use, and history of birth defect-affected pregnancy. All analyses were performed using SPSS package (Version 24.0. IBM Corp., Armonk, NY, USA).

A total of 224 NTD cases and 523 controls were included in analyses from 2010 to 2016. The case group comprised 78 cases of anencephaly, 121 of spina bifida, and 25 of encephalocele. Among 224 NTDs cases, 16 cases (7.1%) had other malformations, such as orofacial clefts or gastroschisis. Compared with healthy control mothers, case mothers had lower education levels, higher gravidity, higher frequency of history of pregnancy affected by birth defects, higher prevalence of contracting fever or flu or having NVP, and lower rates of periconceptional folic acid use. In addition, case mothers were more likely than control mothers to be ≥30 years of age and to be overweight (Pre-pregnancy BMI ≥25 kg/m², Table 1).

Overall, 59.4% (133/224) of case mothers reported exposure to passive smoking during the periconceptional period, compared with 29.4% (154/523) of control mothers. In 2013, we started collecting data on places where passive smoking occurs (e.g., at home, work, or in other public places). There were 87 women who reported the information, of whom 62.1% were exposed to smoke at home. The crude OR of NTDs for passive smoking exposure was 3.502 (95% CI: 2.527–4.853). After adjusting for maternal age, pre-pregnancy BMI, education, fever or flu in early pregnancy, NVP, periconceptional folic acid use, and history of birth defect-affected pregnancy, there was a still strong association, with the adjusted OR being 3.227 (95% CI: 2.213–4.704). Positive dose-response patterns between exposure frequency and risk of NTDs were found, and the adjusted ORs were 1.878 (95% CI: 1.115–3.163), 2.584 (95% CI: 1.348–4.954), and 6.114 (95% CI: 3.673–10.178) for exposure frequency of 1–3, 4–6, and >6 times per week respectively (\(P_{\text{for trend}}<0.001\), Table 2). Analysis of sub-types of NTDs separately showed that anencephaly, spina bifida, and encephalocele were also significantly associated with maternal passive smoking exposure after adjusting for potential confounders (Table 3).

**DISCUSSION**

This study indicated an association between maternal passive smoking during the periconceptional period and an increased risk for both total NTDs and subtypes in offspring of the nonsmoking women, with a significant dose-response relationship. A previous study reported that periconceptional exposure on partner smoking might increase the risk of NTDs in the offspring in same regions from 2002 to 2007 (OR=1.7; 95% CI: 1.3–2.4) (3). Another population-based case-control study consisting of 175 cases and 221 controls among Mexican American women found a similar association between secondhand smoke exposure and NTDs (OR=2.6; 95% CI: 1.6–4.0) (7). Recently, a meta-analysis reported that maternal passive smoking conferred an approximately two-fold risk increase of NTDs (adjusted OR=1.898; 95% CI: 1.557–2.313) (5). These findings were consistent with our study, but the effect was weaker than what we observed in our study (adjusted OR=3.227; 95% CI: 2.213–4.704). This study clarified that higher exposure levels of maternal passive smoking were associated with improved risk for NTDs in offspring, with evidence of a dose-response pattern in nonsmoking women. Most notably, the risk for NTDs rapidly increased to a high level when the exposure frequency was >6 times per week (adjusted OR=6.114; 95% CI: 3.673–10.178).

Maternal exposure to passive smoking during pregnancy increases the risk of adverse pregnancy outcomes (8). In China, female passive smoking is widespread and severe due to the high smoking rates among men, particularly in rural areas. A Chinese study reported the passive smoking exposure rate was 44.9% among 75,107 adults aged ≥40 years (9). The passive smoking exposure proportions recorded in this study were 59.4% in the case group and 29.4% in the control group. The harmful constituents in cigarette smoke can pass through the placenta, including nicotine, carbon monoxide, and polycyclic aromatic hydrocarbons (10). However, most participants are not aware of the health dangers of passive smoking. The WHO FCTC was signed and put into effect in 2006, but unfortunately, tobacco control policies in China are poor and a large gap exists from the FCTC requirements (6). This study suggests that control measures should be taken to prevent tobacco smoke pollution from affecting pregnant women, particularly...
| Characteristic                          | NTDs cases (n=224) * | Controls (n=523)* | P      |
|----------------------------------------|----------------------|-------------------|--------|
|                                        | Number | %  | Number | %  |      |
| Maternal age (years)                   |        |    |        |    | 0.005|
| <25                                    | 82     | 37.6 | 253    | 49.3 |       |
| 25–29                                  | 71     | 32.6 | 161    | 31.4 |       |
| 30–34                                  | 43     | 19.7 | 71     | 13.8 |       |
| ≥35                                    | 22     | 10.1 | 28     | 5.5  |       |
| Prepregnancy BMI (kg/m²)               |        |     |        |     | <0.001|
| <18.5                                  | 21     | 9.7  | 50     | 9.7  |       |
| 18.5–24.9                              | 124    | 57.4 | 364    | 70.8 |       |
| ≥25                                    | 71     | 32.9 | 100    | 19.5 |       |
| Occupation                             |        |     |        |     | 0.094|
| Farmer                                 | 169    | 75.4 | 362    | 69.2 |       |
| Others                                 | 55     | 24.6 | 161    | 30.8 |       |
| Education                              |        |     |        |     | <0.001|
| Primary school or lower                | 18     | 8.1  | 24     | 4.6  |       |
| Junior high school                     | 150    | 67.3 | 284    | 54.6 |       |
| Senior high school                     | 37     | 16.6 | 107    | 20.6 |       |
| College or higher                      | 18     | 8.1  | 105    | 20.2 |       |
| Gravidity                              |        |     |        |     | 0.004|
| 1                                      | 88     | 39.6 | 247    | 47.8 |       |
| 2                                      | 75     | 33.8 | 186    | 36.0 |       |
| ≥3                                     | 59     | 26.6 | 84     | 16.2 |       |
| Parity                                 |        |     |        |     | 0.323|
| Primiparas                             | 120    | 57.1 | 305    | 61.1 |       |
| Multiparas                             | 90     | 42.9 | 194    | 38.9 |       |
| History of birth defect-affected pregnancy |      |     |        |     | <0.001|
| Yes                                    | 12     | 5.5  | 5      | 1.0  |       |
| No                                     | 208    | 94.5 | 507    | 99.0 |       |
| Fever or flu in early pregnancy        |        |     |        |     | <0.001|
| Yes                                    | 84     | 38.7 | 84     | 16.6 |       |
| No                                     | 133    | 61.3 | 421    | 83.4 |       |
| Nausea and vomiting of pregnancy       |        |     |        |     | 0.001|
| Yes                                    | 53     | 24.5 | 73     | 14.2 |       |
| No                                     | 163    | 75.5 | 442    | 85.8 |       |
| Maternal alcohol consumption           |        |     |        |     | 0.078|
| Yes                                    | 23     | 10.3 | 34     | 6.5  |       |
| No                                     | 201    | 89.7 | 487    | 93.5 |       |
| Periconception folic acid use          |        |     |        |     | 0.043|
| Yes                                    | 129    | 58.1 | 337    | 65.9 |       |
| No                                     | 93     | 41.9 | 174    | 34.1 |       |

* Values may not sum to the total numbers because of missing information for some subjects.
Abbreviations: NTDs=neural tube defects; BMI=body mass index.
exposure at home, to minimize the harmful effects of passive smoking exposure in offspring.

This study had several strengths. It was based on a population-based birth-defect surveillance system with a high prevalence of NTDs and a high participation rate. The case and control participants were from the same source population. The passive smoking exposure level was graded, which helped us to assess the association between different exposure levels and the risk of NTDs. Only nonsmoking mothers were selected in the current study, and the effect of passive smoking exposure was unconfounded by maternal active smoking.

This study was also subject to some limitations. Maternal passive smoking was reported mainly by pregnant women and reporting or recall bias may have potential impacts on the results due to the case-control design. It is worth further investigating with deeper passive smoking exposure assessments, especially through biochemical markers such as nicotine levels in maternal urine or umbilical cord blood. Studies that also considered potential gene-environment interaction may be necessary to understand the role of passive smoking exposure in NTDs etiology.

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