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Ambient air pollution the risk of stillbirth: A prospective birth cohort study in Wuhan, China

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ABSTRACT

Background: Recent studies suggest that ambient air pollution exposure during pregnancy is associated with stillbirth occurrence. However, the results on the associations between ambient air pollutants and stillbirths are inconsistent and little is known about the gestational timing of sensitive periods for the effects of ambient air pollutants exposure on stillbirth.

Objective: This study aimed to examine whether exposure to high levels of ambient air pollutants in a Chinese population is associated with an increased risk of stillbirth, and determine the gestational period when the fetus is most susceptible.

Methods: We conducted a population-based cohort study in Wuhan, China, involving 95,354 births between June 10, 2011 and June 9, 2013. The exposure assessments were based on the daily mean concentrations of air pollutants obtained from the exposure monitor nearest to the pregnant women's residence. Logistic regression analyses were performed to determine the associations between stillbirths and exposure to each of the air pollutants at different pregnancy periods with adjustment for confounding factors.

Results: Stillbirth increased with a 10 $\mu g/m^3$ increase in particulate matter 2.5 ($PM_{2.5}$) in each stage of pregnancy, and a significant association between carbon monoxide (CO) exposure and stillbirth was found during the third trimester (adjusted odds ratio (aOR): 1.01, 95% confidence interval (CI): 1.00–1.01) and in the entire pregnancy (aOR: 1.18, 95% CI: 1.04–1.34). Furthermore, an increased risk of stillbirth in the third trimester was associated with a 10 $\mu g/m^3$ increase in PM_{10} (aOR: 1.08, 95% CI: 1.04–1.11), nitrogen dioxide (NO_2) (aOR: 1.13, 95% CI: 1.07–1.21) and sulfur dioxide (SO_2) (aOR: 1.26, 95% CI: 1.16–1.35). However, no positive association was observed between ozone exposure and stillbirth. In the two-pollutant models, $PM_{2.5}$ and CO exposures were found to be consistently associated with stillbirth.

Conclusions: Our study revealed that exposure to high levels of $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO increases the risk of stillbirth and the most susceptible gestational period to ambient air pollution exposure was in the third trimester. Further toxicological and prospective cohort studies with improved exposure assessments are needed to confirm the causal link between air pollutants and stillbirth.

1. Introduction

Stillbirth is currently one of the most unheeded tragedies worldwide (Bhutta et al., 2011). Approximately 2.6 million stillbirths occurred worldwide in 2015, with an approximate stillbirth rate of 18.4 per 1000 total births globally. Data also show that most stillbirths occurred in low-income and middle-income countries (Lawn et al., 2016; Chen et al., 2016). Although significant efforts have been made to reduce the occurrence of stillbirths in the past two decades, China still ranked among the top five countries with the highest number of stillbirths

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globally (Chen et al., 2016; Lawn et al., 2010). Stillbirth, a serious adverse pregnancy outcome, is not yet fully understood, but several studies suggest that the majority of stillbirths are preventable (Lawn et al., 2010; Yakoob et al., 2010). Thus, determining the potential risk factors associated with stillbirth in order to reduce the number of stillbirths continues to be a significant public health priority.

A number of studies indicate a significant association between air pollution exposure during pregnancy and preterm birth, congenital defects, and low birth weight (Estarlich et al., 2016; Agay-Shay et al., 2013; Liang et al., 2014; Yorifuji et al., 2015; Tan et al., 2017). However, few studies have examined the associations between ambient air pollutants and stillbirth, especially in developing countries faced with serious air pollution (Pope et al., 2010; Hwang et al., 2011). Moreover, findings are inconsistent among a few studies that investigated the association between ambient air pollutants and the risk of stillbirth. A study conducted in California concluded that exposure to particulate matter 2.5 ($PM_{2.5}$) and nitrogen dioxide (NO_2) throughout pregnancy was associated with stillbirth occurrence (Green et al., 2015); however, another study in Ohio showed that only exposure to $PM_{2.5}$ during the third trimester of pregnancy was associated with stillbirth (DeFranco et al., 2015). No significant association was found between exposure to $PM_{2.5}$ and stillbirth in a study conducted in New Jersey (Faiz et al., 2012; Faiz et al., 2013).

China experiences serious air pollution problems due to its status as a developing country undergoing continuous industrial and social development. Increasingly, researchers and healthcare professionals are focusing on the health problems caused by air pollution (Chen et al., 2013). The few studies that have explored the association between ambient air pollution exposure and stillbirth in Chinese populations (Hwang et al., 2011; Hou et al., 2014) have had inconsistent results. These studies, conducted over 10 years ago did not specifically examine the connection between stillbirth and $PM_{2.5}$ exposure, which has been confirmed to have severe negative effects on maternal and fetal health (Green et al., 2015; DeFranco et al., 2015) in Western countries. Consequently, we conducted a cohort study involving 95,354 births in Wuhan to evaluate the effects of main ambient air pollutant ($PM_{2.5}$, PM_{10}, sulfur dioxide (SO_2), NO_2, ozone (O_3) and carbon monoxide (CO)) exposure during pregnancy on the risk of stillbirth and to explore the gestational period when the fetus is most susceptible.

2. Materials and methods

2.1. Data sources and study population

A population-based prospective cohort study involving births between June 10, 2011 and June 9, 2013 was conducted using the Wuhan Maternal and Child Health Management Information System from Wuhan Medical and Health Center for Women and Children. The information system was one of the first three standardized information systems in China used for the surveillance of women and children's health and adverse pregnancy outcomes (Xiong et al., 2016; Zhang et al., 2016). It covered nearly 100,000 births per year from most of the maternity units in Wuhan city; all pregnant women in Wuhan were required to register in the system during the first trimester of their pregnancy. The initial registration was performed at a local maternal health care center. Subsequent regular examinations during prenatal care visits were recorded into the system by trained health care workers (Zhang et al., 2016). The information collected by the system included demographic characteristics, medical history, prenatal examinations, prenatal care, deliveries, and postnatal care visits for mothers and infants. The study was approved by the Health Department of Hubei Province and the Institutional Review Board of Wuhan Women and Children Health Care Center.

Data for all live births and stillbirths that occurred in Wuhan while the study was conducted were initially obtained from the Wuhan Maternal and Child Health Management Information System. To limit the study population, only mothers living in the central districts of Wuhan with singleton births occurring at 20–42 weeks of gestation without major congenital anomalies (Green et al., 2015; DeFranco et al., 2015; Faiz et al., 2013) were chosen to participate. The study population consisted of all infants conceived between June 10, 2011 and June 9, 2013, 20 weeks prior to the start of the study period and 42 weeks prior to the end of the study period, to avoid fixed cohort bias. A total of 96,416 births that met the inclusion criteria were initially enrolled; about 95,354 births (98.9%) were included in the analyses after excluding individuals with exposure-related restriction.

2.2. Exposure assessment

All ambient air pollution data for particulate matter ($PM_{2.5}$ and PM_{10}), SO_2, NO_2, CO and O_3 were available from the nine national air quality automatic monitoring stations of the Wuhan Environmental Monitoring Center for the period from June 10, 2011 and June 9, 2013; the national monitoring stations were established in compliance with the monitoring standards of environmental air quality in China and well-distributed around the urban districts of Wuhan (Qian et al., 2016). All available concentrations of PM_{10}, SO_2, NO_2, CO and O_3 were collected automatically and continuously 24 h per day and $PM_{2.5}$ data was collected by manual monitoring method and use the Beta attenuation method to measure the concentration of $PM_{2.5}$. All the initial data were audited and disposed by professional staff of the Wuhan Environmental Monitoring Center; the percentages of the missing data were 1.4% for PM_{10}, 1.5% for SO_2, 2.3% for NO_2, 2.5% for CO, 3.5% for O_3, and 19.5% for $PM_{2.5}$. The main reason for missing data of $PM_{2.5}$ was that we did not operate devices to collect data on rainy days. A daily average concentration was calculated for air pollutants to assess the exposure of pregnant women during the entire study period. In our study population, pregnant women were restricted to those pregnancies with exposure data available on ≥ 1 days of each week, and ≥ 10 days of each month during the pregnancy period. This resulted in 89.0% of the original population for $PM_{2.5}$ and 97.5%–98.9% of the original population PM_{10}, CO, NO_2, SO_2 and O_3 meeting this criterion. The concentrations of air pollutants were assigned to each pregnant woman using the nearest monitor method; in this method, the nearest monitoring station to the pregnant women's residential community was allotted an exposure area of pregnant women (Qian et al., 2016; Zhang et al., 2016). A community refers to the smallest administrative division of the city. A total of 102 communities with the average area of 2 km^2 were involved in this study. The median (minimum-maximum) distance between the nearest monitoring station and the center of the community where pregnant women reside is 3.1 km (0.1–9.7 km) for PM_{10}, SO_2, NO_2, O_3, and CO and 4.6 km (0.1–17.3 km) for $PM_{2.5}$. All pregnant women were organized into communities according to their residential addresses as reported at the first physical examination. The 14th day after the recorded last menstrual period was used to define a pregnant woman and was considered the starting point of her exposure to air pollution. Three different categories of air pollution exposure were constructed to evaluate the associations between air pollutants and stillbirth: First, the monthly average exposure concentration, which was calculated as the mean of all pollutant concentrations during the specific month to assess the exposure level during different months; second, the trimester average pollutant concentration, which was separately calculated as the mean of all available pollutant concentrations in the first, second and third trimesters of pregnancy to assess the exposure level during different phases; third, the average pollutant concentration of the entire pregnancy, which was calculated as the mean of all available daily pollutant concentrations from the first day of pregnancy to delivery to assess the exposure level during the entire pregnancy. Cutoff definitions: entire pregnancy: from first day of conception to delivery; first trimester: first 13 weeks of gestation; second trimester: second 13 weeks of gestation; third trimester: all remaining days of pregnancy. Similar classifications have been adopted in previously