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Maternal exposure to ambient air pollutant and risk of oral clefts in Wuhan, China ☆

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A B S T R A C T

Maternal exposure to ambient air pollution has been related to oral clefts in offspring; however, the epidemiologic evidence is equivocal. Especially, the association between high levels of exposure to ambient air pollution during pregnancy and oral clefts remains unclear. The objective of this study was to evaluate whether high levels of maternal exposure to $PM_{2.5}$, PM_{10}, O_3, CO and SO_2 are related to increased risk of oral clefts in Wuhan, China. A population-based study was conducted using cohort of 105,927 live-born infants, fetal deaths, and stillbirths during a two-year period from 2011 to 2013. For each participant, weekly and monthly averages of daily mean concentrations for each pollutant were estimated. Multiple logistic regression analyses were constructed to quantify the adjusted odds ratios (aORs) for the relationship between each air pollutant and oral clefts while controlling for key covariates. Using monthly averages, a cleft lip with or without cleft palate (CLP) was associated with $PM_{2.5}$ ($aORs_{\text{2nd month}} = 1.34$, CI:1.19–1.49; $aORs_{\text{3rd month}} = 1.14$, CI:1.02–1.28), PM_{10} ($aORs_{\text{2nd month}} = 1.11$, CI:1.00–1.23) and CO ($aORs_{\text{2nd month}} = 1.31$, CI:1.14–1.51; $aORs_{\text{3rd month}} = 1.17$, CI:1.03–1.33). A cleft palate only (CPO) was associated with $PM_{2.5}$ ($aORs_{\text{2nd month}} = 1.24$, CI: 1.03–1.48), and O_3 ($aORs_{\text{2nd month}} = 1.21$, CI: 1.03–1.42; $aORs_{\text{3rd month}} = 1.18$, CI: 1.02–1.37). Our findings reveal an association between air pollutants exposure and the risk of oral clefts. Future studies are needed to confirm these associations, and clarify the causality related to specific pollutants during the most relevant vulnerable exposure time windows for oral clefts during pregnancy.

1. Introduction

An increasing number of epidemiologic studies have examined the effects of ambient air pollutants on adverse birth outcomes during pregnancy (Craig et al., 2009; Ritz et al., 2002; Sapkota et al., 2012; Stieb et al., 2012). Currently, there are few studies that have investigated the association between specific congenital anomalies and air pollution (Padula et al., 2013; Ajit Rao et al., 2016; Ritz et al., 2002; Stingone et al., 2014). While the results from these few studies are inconsistent or inconclusive (Qian et al., 2016; Shah and Balkhair, 2011; Sram et al., 2005), these preliminary results have indicated that maternal exposure to O_3 and $PM_{2.5}$ may increased the risk of congenital heart defects (CHDs) (Bin Zhang et al., 2016b; B. Zhang et al., 2016). These results lead to questions about whether maternal air pollution exposure could increase the risk of other birth defects, such as oral clefts. Mechanistically, air pollution may

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influence the skeletal malformation development via oxidative stress, toxicity to certain cell populations, anoxic events, and hemodynamic during development (Hwang and Jaakkola, 2008). These potential biomechanisms provide biological rationale to evaluate the relationship between environmental toxins and oral clefts.

An oral cleft is one of the most common congenital anomalies. This anomaly is usually divided into two different types based on the differences in the embryological pathogens: a cleft palate only (CPO) and a cleft lip with or without cleft palate (CLP) (Arosarena, 2007). Genetic and environmental factors contribute a vital part to the etiology of oral clefts (Leslie and Marazita, 2013; Zeiger et al., 2005). A group of suspected risk factors have been elucidated in the disease causal pathway, including maternal smoking (Lie and Vindenes, 2008), alcohol consumption (Lorente et al., 2000), folic acid deficiencies (Wehby and Murray, 2010), drugs usage (antiepileptic, topiramate, corticosteroid) (Abrishamchian et al., 1994; Margulis et al., 2012; Pradat et al., 2003), and maternal infections (rubella, toxoplasmosis, cytomegalovirus, herpes simplex TORCH) (Dixon et al., 2011; Ajit Rao et al., 2016).

Increasing evidence suggests that air pollution is also a risk factor in the etiology for oral clefts, and previous epidemiologic studies have linked oral clefts with ambient air pollution; however, these studies reported mixed findings. The Taiwan study showed an association between CLP and O_3 exposure (Hwang and Jaakkola, 2008); the Brisbane study showed increased odds of CLP with higher exposure to SO_2 (Craig et al., 2009); the New Jersey's studies found limited evidence of an associations between CPO and O_3 exposure as well as between CLP and SO_2 exposure (Marshall et al., 2010); the four U.S states study found CPO was associated with $PM_{2.5}$ exposure (Zhou et al., 2017); and the U.S study collected data from the 19 hospitals found an association between CPO and CO, CPO and PM_{10}, and between CLP and SO_2 (Zhu et al., 2015). Contrarily, studies conducted in England (Rankin et al., 2009), Barcelona (Schembari et al., 2014), and California (Padula et al., 2013; Ritz et al., 2002) reported no association between ambient air pollutants and oral clefts. Two meta-analyses summarized risk estimates for pollutants exposure and risk of CLP and CPO, and neither reached statistical significance (Chen et al., 2014; Vrijheid et al., 2011). Another recent meta-analysis reported that ozone exposure during pregnancy was significantly associated with CLP (Ajit Rao et al., 2016). However, these meta-analyses did not cover the studies of $PM_{2.5}$ during pregnancy. In addition, few studies have been conducted in Asia (see Supplementary Material, Table S1).

To further understand the relationship between environmental exposure and oral clefts, we use extant data consisting of 105,927 offspring among women residing in Wuhan, which is the largest city in central China. Since Wuhan experiences high levels of air pollutants exposure, our study provides an opportunity to examine the relationship between air pollutants exposure and the risk of developing CLP and CPO in newborn children.

2. Materials and methods

2.1. Study population

This is a prospective population-based cohort study. The study population included mother-infant pairs from Wuhan Maternal and Child Health Management Information System (WMCHMIS), which has approximately 100,000 annual births (including rural and urban areas). All births in Wuhan are compulsorily reported to the WMCHMIS within 24 h of delivery. The WMCHMIS includes electronic records collected prospectively from the first prenatal care visit to postnatal period and strictly adheres to a standardized quality assurance and quality control process to ensure high data quality. The study included pregnant women living in the urban areas of Wuhan from June 2011 to June 2013, and included births of live-born, stillbirths, and fetal deaths. One of the main purposes of WMCHMIS is to monitor adverse birth outcomes, such as birth defects. We collected all cases of CLP and CPO in urban areas of Wuhan and included those among live births and stillbirths between 20 and 41 weeks of gestation as confirmed by clinical and autopsy reports. Gestational age was assessed based on the last menstrual period date.

We collected data for 108,167 births in this study. Of these, 960 were excluded because of the presence of known chromosome abnormalities and other organ systems malformations. Furthermore, 1280 were excluded for incomplete information of maternal residence. A total of 105,927 mother-infants pairs were enrolled, and of these 133 infants were diagnosed with oral clefts at birth.

The Health Department of Wuhan City, as well as, the Institutional Review Board at Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital) approved this study protocol.

2.2. Maternal exposure assessment

During our study period of 2011–2013, complete monitoring data of $PM_{2.5}$, PM_{10}, O_3, SO_2 and CO, as well as daily air pressure, humidity and temperature are available from nine national air quality monitor stations of Wuhan Environmental Monitoring Center. These monitor stations were mainly located in the urban areas of Wuhan. The collection of air pollutants and the installation of air quality monitoring stations were in strict accordance with the monitoring rules on environmental air quality in China. (Zhao et al., 2016). The measurements have been collected continuously and automatically.

We used the nearest monitor station approach to estimate exposure based on the maternal residences reported at the time of the woman's first prenatal care visit during the first trimester of pregnancy. A map of the study area of monitor locations was reported elsewhere (Bin Zhang et al., 2016a). The relevant embryologic period for oral cleft is between the 4th and 12th week of gestation (Hwang and Jaakkola, 2008; Wyszynski and Wu, 2002). Thus, we focused on the first trimester of pregnancy for the collection of pollution data. We calculated 24-hour averages for CO, SO_2, $PM_{2.5}$, and PM_{10}, and a maximum 8-hour average for O_3. Monthly and weekly average values for CO, NO_2, O_3, SO_2, $PM_{2.5}$, and PM_{10}, as well as for the air temperature, the humidity, and the air pressure were assigned for each woman. The exposure was classified at the individual level. The median distance between the mother's residence community center and the nearest stations was 5.9 km (0.3–11.5 km) for $PM_{2.5}$ and 3.1 km (0.1–6.0 km) for PM_{10}, CO, O_3, and SO_2.

2.3. Statistical methods

A multivariable logistic regression analysis was used to assess the associations between each contaminant and the two outcomes (CLP and CPO). Analyses for CLP and CPO were carried out separately. The relationships between our outcomes of interest (CLP and CPO) and environmental exposure were assessed by each trimester and by weeks of pregnancy (first 12 weeks only). Based on the existing literature and the study population characteristics, we collected variables suspected as potential confounders from the WMCHMIS. These potential confounders included the maternal age at delivery, the sex of infants, the season of conception, education levels, parity, and residential addresses (Hwang and Jaakkola, 2008; Zhou et al., 2017). Mothers' marital status and race were not controlled for because 99.9% of the mothers were married and