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

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Abstract
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 PM2.5, PM10, O3, CO and SO2 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 PM2.5 (aORs 2nd month = 1.34, CI:1.19–1.49; aORs 3rd month = 1.14, CI:1.02–1.28), PM10 (aORs 2nd month = 1.11, CI:1.00–1.23) and CO (aORs 2nd month = 1.31, CI:1.14–1.51; aORs 3rd month = 1.17, CI:1.03–1.33). A cleft palate only (CPO) was associated with PM2.5 (aORs 2nd month = 1.24, CI:1.19–1.49; aORs 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.

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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; Ajiit 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 O3 and PM2.5 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...
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 (Webby and Murray, 2010), drugs usage (anti-epileptic, 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 O3 exposure (Hwang and Jaakkola, 2008); the Brisbane study showed increased odds of CLP with higher exposure to SO2 (Craig et al., 2009); the New Jersey's studies found limited evidence of an associations between CPO and O3 exposure as well as between CLP and SO2 exposure (Marshall et al., 2010; the four U.S states study found CPO was associated with PM2.5 exposure (Zhou et al., 2017); and the US study collected data from the 19 hospitals found an association between CPO, CO, CPO and PM10, and between CLP and SO2 (Zhu et al., 2015). Contrarily, studies conducted in England (Rankin et al., 2009), Barcelona (Schembri 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 PM2.5 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 PM2.5, PM10, O3, SO2 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, SO2, PM2.5, and PM10, and a maximum 8-hour average for O3. Monthly and weekly average values for CO, NO2, O3, SO2, PM2.5, and PM10, 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 PM2.5 and 3.1 km (0.1–6.0 km) for PM10, CO, O3, and SO2.

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
99.0% of the mothers indicated that they were of the Han ethnic group. Maternal smoking and alcohol use during pregnancy were not controlled for because <0.7% of the mothers were smokers and <0.5% of the mothers were drinkers.

In the final models, we adjusted for maternal ages (classified as <20, 20–25, 25–30, >30 years), education levels (classified as middle school or below, high school/technical school/vocational school, bachelor’s or higher degree), infant sexes (males or females), parities (classified as 1 = first-born children and > 1 = mothers with a previous birth), the season of conception (classified as spring, summer, fall and winter), the air temperature, the humidity, and the air pressure. Additionally, the associations between each pollutant and the risk of CPL/CPO by month or week of pregnancy were presented as adjusted odds ratios (aORs) per 10-μg/m³ change for O₃, SO₂, PM₂.₅, and PM₁₀ and per 100-μg/m³ change for CO, along with their respective 95% CIs. The statistical software SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) was utilized for all data analysis, and P < 0.05 was considered statistically significant.

3. Results

3.1. Descriptive statistics

Among 105,927 births, we identified 133 with oral clefts, and 105,794 without any malformations during the study period (Table 1). The prevalence rate of CPL was 8 per 10,000, and CPO was 4.0 per 10,000. Births with an oral cleft were more likely to come from mothers with a lower education as compared to the non-malformed (p < 0.05).

The distributions of the concentrations from the nearest monitor station were shown in Table S1 (see Supplementary Material). The mean exposure concentration of the air pollutants and the corresponding range (25th to 75th percentile range) was 65.61 μg/m³ (37.80–85.04 μg/m³) for PM₂.₅, 107.13 μg/m³ (59.17–134.00 μg/m³) for PM₁₀, 38.54 μg/m³ (18.00–53.91 μg/m³) for SO₂, 72.41 μg/m³ (31.97–106.00 μg/m³) for O₃, and 1.02 mg/m³ (0.70–1.27 mg/m³) for CO.

3.2. Correlations of air pollution exposure and risk for oral cleft

Table 2 shows the aORs and 95% Confidence interval (CIs) for the risk of oral clefts in relation to O₃, CO, SO₂, PM₂.₅, and PM₁₀ exposure for the first trimester of pregnancy. We observed a positive association between all oral clefts and PM₂.₅ particularly in the second month of pregnancy (aORs = 1.29 per 10 μg/m³ change; 95% CI: 1.17–1.42), and in the third month of pregnancy (aORs = 1.11; 95% CI: 1.01–1.22). Furthermore, the risk of having a baby with an oral cleft may increases by 11–29% for the range of PM₂.₅ concentrations considered in this study. Significant associations were observed between PM₂.₅ exposure and both outcomes (CPO and CPL). Similarly, there were significant associations between the outcome CLP and O₃ as well as PM₁₀ exposure. A similar significant association was also observed between CO exposure and CPO. These associations occurred in different months during the windows of susceptibility. No significant associations were observed between CLP, CPO, and SO₂ during the first three month; however, an inverse association between an oral cleft and SO₂ in the third month of pregnancy was observed (aORs = 0.82, 95% CI: 0.58–0.99).

Fig. 1 shows the estimated aORs with their 95% CIs for the relationships between O₃, CO, SO₂, PM₂.₅, and PM₁₀ weekly exposure to the risk of oral clefts, CLP, and CPO (see Supplementary Material, Table S2, for corresponding numerical data). These associations occurred in different weeks during the windows of susceptibility. The risk of oral cleft showed variability across the first 12 weeks of pregnancy. Specifically, PM₂.₅ exposures after 3 weeks of pregnancy, particularly during weeks 4–9, may be associated with a greater susceptibility to developing an oral cleft and for developing a CLP and a CPO. During weeks 4–9, the aORs for CLP per 10-μg/m³ change in PM₂.₅ exposure ranged from 1.09 to 1.22; during weeks 8–9, the aORs for CPL was 1.11. We also observed positive associations for PM₁₀ exposure and oral clefts and CLP in week 8; for CO exposure and oral cleft and CLP in weeks 7, 8, 10, and 11; and for O₃ exposure and oral clefts and CPO in weeks 2, 5, 6, 11 and 12. Although a higher risk from exposure during susceptible windows (4th and 12th week) has been proposed, we didn’t find consistent weeks that could be identified as the critical exposure windows between air pollution and oral clefts.

4. Discussion

Recent studies have found some associations between ambient air pollutants exposures and oral clefts (Craig et al., 2009; Hwang and Jaakkola, 2008; Marshall et al., 2010; Zhou et al., 2017). However, the epidemiologic evidence for the relationship between specific air pollutants and oral clefts is still limited. In our large population-based cohort study, we observed increased odds with increasing PM₂.₅, PM₁₀, O₃, and CO exposure for an oral cleft in the most susceptible periods among Chinese women and infants. These
results add to the evidence of ambient air pollution and oral clefts.

We observed inconsistencies between findings. In previous studies conducted in Southern California, investigators found no significant relationship between any of the pollutants and the risk of oral clefts, but they found an inconsistent elevation in risk related for CO (Ritz et al., 2002). The Taiwan study, using a case-control design, found an association between O3 and CLP during the first two months of pregnancy (aORs 2nd month = 1.20, 95% CI: 1.02–1.39; aORs 3rd month = 1.25, 95% CI: 1.03–1.52), but not to other ambient air pollutants. (Hwang and Jaakkola, 2008). The Brisbane study used the nearest monitor approach, and found increased odds of CLP to the adverse effects caused by environmental factors may be difficult to detect in further study.

Some studies suggested particular exposure periods related to greater susceptibility to certain defects within the window of fetal development may exist. In the current study, we used the monthly averages of exposure, and also used weekly averaged measurements to fully reflect the sensitive time-windows for susceptibility. Some previous studies estimated averages over 3–8 weeks of pregnancy, while other studies averaged air pollution levels by month, trimester, or annual; however, these time periods could fail to capture the temporal variability of exposure. Few studies examined the weekly exposure to air pollution and oral clefts, and gave additional insight into the potential changes for week-specific sensitive windows of development (Zhu et al., 2015). A plausible explanation for this attenuating or masking of association is that the timing of environmental influences for the development of certain defects is narrow and precise. Thus, the summary measures method may not have been sensitive enough to identify the associations (Craig et al., 2009). Moreover, the windows of susceptibility to the adverse effects caused by environmental factors may be inconsistent with the established stages of the embryologic period for the oral clefts development (Stingone et al., 2014).

Like other studies, slightly inverse associations were also found for ambient air pollution and oral clefts. Hansen et al. have found negative associations between PM10 exposure and CPO (Craig et al., 2009). Padula et al. reported an inverse association between CO concentration and CLP (Padula et al., 2013). Ritz et al. showed higher CO exposure associated with decreased odds of CPO during the third month of pregnancy (Ritz et al., 2002). Our results also showed inverse associations between SO2 exposure and oral cleft during the third month of pregnancy. These effects are difficult to

Table 2
Adjusted odds ratios and 95% CI for Oral Cleft and exposure to ambient air pollution during the first 3 months of pregnancy.

<table>
<thead>
<tr>
<th>Pollutant</th>
<th>Oral cleft (n = 133)</th>
<th>Cleft lip with or without cleft palate (n = 90)</th>
<th>Cleft palate only (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st M</td>
<td>1.03 (0.91–1.16)</td>
<td>1.09 (0.95–1.25)</td>
<td>0.84 (0.68–1.03)</td>
</tr>
<tr>
<td>2nd M</td>
<td>1.29 (1.17–1.42)</td>
<td>1.34 (1.19–1.49)</td>
<td>1.24 (1.03–1.48)</td>
</tr>
<tr>
<td>3rd M</td>
<td>1.11 (1.01–1.22)</td>
<td>1.14 (1.02–1.28)</td>
<td>1.13 (0.97–1.33)</td>
</tr>
<tr>
<td>PM10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st M</td>
<td>0.93 (0.85–1.01)</td>
<td>0.98 (0.88–1.08)</td>
<td>0.78 (0.64–1.01)</td>
</tr>
<tr>
<td>2nd M</td>
<td>1.07 (0.98–1.17)</td>
<td>1.11 (1.00–1.23)</td>
<td>0.99 (0.84–1.16)</td>
</tr>
<tr>
<td>3rd M</td>
<td>0.96 (0.89–1.04)</td>
<td>0.95 (0.86–1.04)</td>
<td>0.99 (0.86–1.13)</td>
</tr>
<tr>
<td>O3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st M</td>
<td>1.10 (0.99–1.21)</td>
<td>1.07 (0.95–1.20)</td>
<td>1.16 (0.97–1.38)</td>
</tr>
<tr>
<td>2nd M</td>
<td>1.12 (1.02–1.22)</td>
<td>1.07 (0.96–1.19)</td>
<td>1.21 (1.03–1.42)</td>
</tr>
<tr>
<td>3rd M</td>
<td>1.02 (0.93–1.11)</td>
<td>0.93 (0.84–1.04)</td>
<td>1.18 (1.02–1.37)</td>
</tr>
<tr>
<td>SO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st M</td>
<td>0.81 (0.64–1.02)</td>
<td>0.81 (0.61–1.06)</td>
<td>0.77 (0.51–1.16)</td>
</tr>
<tr>
<td>2nd M</td>
<td>0.94 (0.77–1.15)</td>
<td>0.99 (0.77–1.26)</td>
<td>0.83 (0.59–1.17)</td>
</tr>
<tr>
<td>3rd M</td>
<td>0.82 (0.68–0.99)</td>
<td>0.85 (0.68–1.07)</td>
<td>0.79 (0.58–1.08)</td>
</tr>
<tr>
<td>CO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st M</td>
<td>0.95 (0.85–1.06)</td>
<td>0.97 (0.84–1.11)</td>
<td>0.40 (0.05–3.10)</td>
</tr>
<tr>
<td>2nd M</td>
<td>1.24 (1.11–1.40)</td>
<td>1.31 (1.14–1.51)</td>
<td>1.16 (0.94–1.42)</td>
</tr>
<tr>
<td>3rd M</td>
<td>1.10 (0.99–1.22)</td>
<td>1.17 (1.03–1.33)</td>
<td>0.99 (0.83–1.19)</td>
</tr>
</tbody>
</table>

All values in bold are significant at p < 0.05.

* a Adjusted for maternal age, education, parity, infant sex, season of conception, temperature, humidity and air pressure.
* b 1st M = The first month exposure.
* c 2nd M = The second month exposure.
* d 3rd M = The third month exposure.

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Fig. 1. Estimated adjusted OR and 95% CIs of Oral Cleft for continuous measures of 1-week averages of daily measures of air pollutants, plotted for weeks 1–12 pregnancy. CI, confidence interval; OR, odds ratio.
explain and may be due to confounding by environmental exposures, socio-demographic factors, methodological limitations, or by chance. One reason could partially explain these inverse effects is that excessive toxin exposure during pregnancy may lead to competing outcomes or affect the survival of fetuses such as early abortion. (Ritz et al., 2002).

The bio-mechanism that explains how maternal exposure to air pollutants may lead to oral clefts is still unclear. Toxicological data from animal studies provides biologically a plausible explanation for the potential teratogenicity of air pollutants. For instance, exposure to O3 could lead to oxidative stress by forming free radicals (Mccullough, 2015), and demonstrated embryotoxicity in rats (Kavlock, 1977); exposure to SO2 could cause oxidative damage and induced multiple organ malformations in mice (Meng, 2003); and PM2.5 could cross the placenta (Saenen et al., 2015), and formed DNA adducts, which could lead to genetic toxicity (Li et al., 2014). Other studies revealed associations of air pollutants with inflammation (Forbes et al., 2009), coagulation (Bind et al., 2012), immune dysregulation (Capon et al., 2003), anoxic events, and hemodynamic during development (Hwang and Jaakkola, 2008). If these toxic effects occur during the critical period of embryonic development, it may lead to oral clefts.

The current study has several major strengths. The population size examined in this study was bigger than in previous Chinese studies. The larger sample size could reduce selection bias and random error, which are common in small sample size studies. Furthermore, data of oral clefts were collected from a citywide population-based monitoring program, which supplied relatively dependable and complete data on birth defects. In order to reduce the measurement error, we used maternal residence during the early pregnancy rather than the residence at the birth, and the residential mobility was 2.6% in our study, which was lower than the previous studies (Zhou et al., 2017; Zhu et al., 2015). This study was also able to estimate weekly exposure during the first trimester of pregnancy to reveal temporal variability in the associations between oral clefts and air pollution.

This study has a number of limitations. There is potential measurement error in the exposure assignment based on the nearest monitoring station to the mothers’ residence. In common with most studies, we lacked indoor air pollution data and its correlation with outdoor air pollution levels. Exposure misclassification would bias results in an unknown direction. The reported date of the last menstrual period may cause misclassification of timing of exposure. Because women may not remember their LMP date, which could cause LMP to be unreliable. In addition, we have no data on other variables that may confound the observed relationships, such as exposure to passive smoking and socio-demographic factors.

5. Conclusion

Our study found that ambient PM2.5, PM10, O3, and CO exposure during the first trimester of pregnancy was associated with increased risk of CLP/CPO. Future epidemiological studies are still needed to confirm these associations and clarify the causality related to specific pollutants during the most relevant vulnerable exposure windows of pregnancy.

Author contributions

BZ QZ YD TZ conceived and designed the study. JZ wrote the main manuscript text. JZ analyzed the data. QZ SY SL HR RB SJ edited the manuscript. SX provided statistical support. HM YZ interpreted data and results. KY YT collected and organized data. All authors reviewed the manuscript.

Competing financial interests

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envpol.2018.03.053.

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