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Maternal exposure to ozone and $PM_{2.5}$ and the prevalence of orofacial clefts in four U.S. states

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ABSTRACT

Background: While there is some evidence that maternal exposure to ambient air pollution is associated with orofacial clefts in offspring, the epidemiologic studies have been largely equivocal. We evaluated whether maternal exposure to elevated county-level ambient fine particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) and ozone during early gestation was associated with a higher prevalence of orofacial clefts.

Methods: Birth data consisting of 4.7 million births from 2001 to 2007 were obtained from National Birth Defects Prevention Network for four states — Arizona, Florida, New York (excluding New York City), and Texas. The air pollution exposure assessment for gestational weeks 5–10 was based on county-level average concentrations of $PM_{2.5}$ and ozone data generated using a Bayesian fusion model available through CDC's Environmental Public Health Tracking Network. Two outcomes were analyzed separately: cleft lip with or without cleft palate, cleft palate alone. In logistic regression analyses, we adjusted for factors that were suspected confounders or modifiers of the association between the prevalence of orofacial clefts and air pollution, i.e., infant sex, race-ethnicity, maternal education, smoking status during pregnancy, whether this was mother's first baby, maternal age.

Results: Each 10 μg/m^3 increase in $PM_{2.5}$ concentration was significantly associated with cleft palate alone (OR =1.43, 95% CI: 1.11–1.86). There was no significant association between $PM_{2.5}$ concentration and cleft lip with or without cleft palate. No associations were observed between ozone exposure and the two outcomes of orofacial clefts.

Conclusions: Our study suggests that $PM_{2.5}$ significantly increased the risk of cleft palate alone, but did not change the incidence of cleft lip with or without palate. Ozone levels did not correlate with incidence of orofacial clefts.

1. Introduction

Orofacial clefts are complex malformations of the lip and/or palate that result from improper fusion of tissues during early embryologic development (Arosarena, 2007). Due to the distinct developmental origins of the lip and primary palate from the secondary palate, orofacial clefts can be subdivided into cleft lip with or without cleft palate (CL+/-CP) and cleft palate alone (CP). In the United States, CL +/-CP occurs in 1 in 940 live births, whereas CP affects 1 in 1,600 live births (Canfield, 2006; Parker, 2010). Additionally, CL+/-CP and CP may differ in terms of risk factor profiles (Genisca, 2009). Overall, children with orofacial clefts frequently need lifelong multidisciplinary

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care and experience significant morbidity. In spite of the high prevalence of these malformations relative to other birth defects and the clinical significance of these conditions, the etiology of these defects is not well understood, in part because orofacial clefts have considerable genetic heterogeneity (Marazita, 2012; Leslie and Marazita, 2013; Seto-Salvia and Stanier, 2014).

As maternal smoking is considered a well-established risk factor for orofacial defects (Honein, 2007; Little et al., 2004), there is growing concern that maternal exposure to air pollution, which has several of the same chemical constituents as cigarette smoke, such as fine particulate matter with aerodynamic diameter ≤2.5 μm ($PM_{2.5}$) (Invernizzi, 2004), may also be associated with orofacial clefts in offspring. However, to date, the epidemiologic evidence is equivocal. One study in Taiwan determined maternal exposure to ozone was associated with orofacial clefts (Hwang and Jaakkola, 2008). Another study in Australia showed a weak association between sulfur dioxide (SO_2) exposure and orofacial clefts (Hansen, 2009). Also, several U.S. studies (in California, Texas, New Jersey, and Florida) reported no association between the criteria air pollutants evaluated and orofacial clefts (Ritz et al., 2002; Gilboa et al., 2005; Marshall et al., 2010; Tanner et al., 2015; Padula et al., 2013). Recently, a study covering multiple regions in the United States found that exposure to several criteria air pollutants during preconception and early gestation was associated with elevated odds for CP, while CL+/-CP was only associated with preconceptional SO_2 exposure (Zhu et al., 2015). Two recent meta-analyses concluded that there was no association between ambient air pollution and risk of orofacial clefts (Vrijheid et al., 2011; Chen et al., 2014). Another recent meta-analysis found ozone to have the strongest correlation with cleft lip and cleft palate anomalies (Rao et al., 2016). However, the studies reviewed in this meta-analysis overall showed an inconsistent correlation between orofacial clefts and air pollutants, including protective effect. Inconsistencies in this literature may be due to differences in 1) pollutants included, e.g., whether $PM_{2.5}$ was included; 2) pollution levels across populations and how they were estimated, e.g., whether monitored or modeled data were used; and 3) varying sample sizes.

We sought to further assess this association using data from the National Birth Defects Prevention Network (NBDPN) (NBDPN, 2015) and the Environmental Public Health Tracking Program at the Centers for Disease Control and Prevention (CDC) (EPHTN, 2015). Specifically, we evaluated whether maternal exposure to elevated levels of $PM_{2.5}$ and ozone during early pregnancy is associated with a higher prevalence of orofacial defects among offspring.

2. Methods

2.1. Study design and study population

We conducted a retrospective study based on de-identified birth data consisting of 4.7 million births from 2001 to 2007 for four of the states contributing data to the NBDPN— Arizona, Florida, New York (excluding New York City), and Texas. Note that New York City's data were managed separately and we did not have access to them. All births with CL+/-CP or CP and included in the birth defects surveillance programs from these four states were initially eligible for this analysis, and comprised the numerators for the prevalence calculations. The category of CL+/-CP includes cleft lip with or without an associated cleft hard or soft palate, cleft alveolar ridge, and cleft gum (ICD-9-CM codes of 749.1 and 749.20–749.25; CDC/BPA codes of 749.10–749.19 and 749.20–749.29). The category of CP alone comprises cleft hard or soft palate that is not associated with a cleft lip (ICD-9-CM codes of 749.0; CDC/BPA codes of 749.00–749.09). Due to the availability of air pollution data, only births with the start of week 5 of gestation on or after January 1, 2001 were included in the analysis. Also, we excluded all births with week 5 of gestation on or after April 15, 2007, to avoid including only preterm births in this analysis for babies conceived toward the end of our study period.

The base population (i.e., denominator data) included all resident live births in Arizona, Florida, New York (excluding New York City), and Texas. All state data were obtained from the NBDPN (NBDPN, 2015), which facilitated collection of participating state-based birth defects surveillance data (Canfield et al., 2006, 2014; Wang et al., 2015). These data are securely stored at CDC for the purposes of conducting analyses of pooled data. This study protocol was reviewed and approved by the participating states' Institutional Review Boards, as necessary.

The spatial resolution for all births and birth defects data is the county of maternal residence at delivery. The original temporal resolution for data is the month. Because we were using de-identified data, we had access only to the month and year of birth (and not the specific date); therefore, we assumed all births occurred on the 15th day of the birth month. We then estimated the first week of gestation by subtracting the clinical gestational age in completed weeks from the 15th of the month of birth. To match with air pollution data, we used the gestational window of interest of weeks 5–10, which is the most critical period of development of the palate, as palatogenesis begins during the 5th week and the development of the palate is not completed until the 12th week (Merritt, 2005; Moore, 2003). We matched the county information of maternal residence at delivery with the air pollution data to estimate maternal exposure to $PM_{2.5}$ and ozone during the gestational window of interest.

In order to reduce heterogeneity among cases with orofacial clefts, we excluded any oral cleft case or birth with a birth weight < 750 g, plurality ≥2, maternal age < 15 years or > 45 years, or gestational age < 20 weeks from our analysis. As a result, the proportion of cases excluded were 5% for AZ and FL, 6% for NY, and 9% for TX. About 4–5% of the live births were excluded in each of the four states because of these restrictions. In addition, about 6% of observations had missing values for the response or explanatory variables, and hence were not included in the regression analysis.

2.2. Air pollution data

To estimate exposure during weeks 5–10 of gestation, we used average daily $PM_{2.5}$ and ozone modeling data at the census tract level generated by the U.S. Environmental Protection Agency (EPA) for CDC's EPHT Network (EPHTN, 2015). A Bayesian downscaler model (i.e., Bayesian space-time downscaling fusion model) was used to generate these data (Berrocal et al., 2012). It uses air quality monitoring data from U.S. EPA's Air Quality System (AQS), as well as model simulations from the Models-3/Community Multiscale Air Quality (CMAQ), as model inputs (EPA, 2012). Note that CMAQ is a state-of-the-science Eulerian grid model, which has capabilities to simulate the various chemical and physical processes important for understanding atmospheric processes (Byun and Schere, 2006).

We used the $PM_{2.5}$ and ozone predictions generated by the Bayesian downscaler model for two reasons. First, these data provide complete spatial and temporal coverage for the entire contiguous United States. As a comparison, ambient monitoring data from AQS (EPA, 2014) are available only in a limited number of counties (EPA, 2014). In 2005 for example, fewer than 20% of counties in the contiguous United States were monitored for $PM_{2.5}$, and most monitors operated every third day. Second, compared with Bayesian melding and ordinary kriging, predictions from this Bayesian downscaler model have been shown to have better performance, e.g., better calibrated, predictive intervals have empirical coverage closer to the nominal values (Berrocal et al., 2010).

The spatial resolution for all births and birth defects data is the county of maternal residence at delivery. We aggregated the census tract-level air pollution predictions from the downscaling fusion model data to the county level and used that to estimate the mothers' exposure during gestation weeks 5–10. County-level pollution estimates were generated in two ways: simple average and population