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Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects

Yeyi Zhu [a], Cuilin Zhang [a], Danping Liu [b], Katherine L. Grantz [a], Maeve Wallace [a], Pauline Mendola [a,*]

[a] Epidemiology Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD, USA

[b] Biostatistics and Bioinformatics Branch, Division of Intramural Population Health Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Rockville, MD, USA

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ABSTRACT

Background: Maternal air pollution exposure has been related to orofacial clefts but the literature is equivocal. Potential chronic preconception effects have not been studied.
Objectives: Criteria air pollutant exposure during three months preconception and gestational weeks 3–8 was studied in relation to orofacial defects.
Methods: Among 188,102 live births and fetal deaths from the Consortium on Safe Labor (2002–2008), 63 had isolated cleft palate (CP) and 159 had isolated cleft lip with or without cleft palate (CL $\pm$CP). Exposures were estimated using a modified Community Multiscale Air Quality model. Logistic regression with generalized estimating equations adjusted for site/region and maternal demographic, lifestyle and clinical factors calculated the odds ratio (OR) and 95% CI per interquartile increase in each pollutant.
Results: Preconception, carbon monoxide (CO; OR=2.24; CI: 1.21, 4.16) and particulate matter (PM) ≤ 10 μm (OR=1.72; CI: 1.12, 2.66) were significantly associated with CP, while sulfur dioxide (SO_2) was associated with CL $\pm$CP (OR=1.93; CI: 1.16, 3.21). During gestational weeks 3–8, CO remained a significant risk for CP (OR=2.74; CI: 1.62, 4.62) and nitrogen oxides (NO_x; OR=3.64; CI: 1.73, 7.66) and PM ≤ 2.5 μm ($PM_{2.5}$; OR=1.74; CI: 1.15, 2.64) were also related to the risk. Analyses by individual week revealed that positive associations of NO_x and $PM_{2.5}$ with CP were most prominent from weeks 3–6 and 3–5, respectively.
Conclusions: Exposure to several criteria air pollutants preconception and during early gestation was associated with elevated odds for CP, while CL $\pm$CP was only associated with preconception SO_2 exposure.

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1. Introduction

A steadily growing body of literature has implicated maternal exposure to air pollution as a potential causal factor in offspring adverse birth outcomes, including infant mortality, low birthweight, and preterm birth (Proietti et al., 2013; Shah et al., 2011; Stieb et al., 2012). Emerging data also suggests a link between air pollution and congenital anomalies (E.K. Chen et al., 2014; Vrijheid et al., 2011). A leading cause of infant mortality (Matthews and MacDorman, 2013), congenital anomalies also contribute significantly to childhood and adult morbidity. Moreover, given that ambient air pollution affects large populations and is difficult to modify at the individual level, it is of great public health significance to improve our understanding of the associations between air pollutants and congenital anomalies.

Orofacial defects (i.e., cleft palate and cleft lip with or without cleft palate) are common but have received less attention than congenital heart defects in studies of air pollution. Positive associations between air pollutants and orofacial defects have been observed (Gilboa et al., 2005; Hansen et al., 2009; Hwang and Jaakkola, 2008; Marshall et al., 2010), but no significant pooled associations were found in meta-analyses (E.K. Chen et al., 2014; Vrijheid et al., 2011). The overall null associations may be attributable to the heterogeneity in outcome ascertainment and exposure assessment, varied confounders, and the small number of studies.

Among the nine previous studies on air pollution and orofacial clefts, eight were single-region studies with relatively small geographic coverages (Gilboa et al., 2005; Hansen et al., 2009; Hwang and Jaakkola, 2008; Marshall et al., 2010; Padula et al., 2013;

* Corresponding author.
E-mail address: pauline.mendola@nih.gov (P. Mendola).

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Rankin et al., 2009; Ritz et al., 2002; Schembari et al., 2014) except for one covering four regions in England (Dolk et al., 2010). In addition, most previous studies averaged air pollutant levels over the organogenesis period from gestational weeks 3–8 (Gilboa et al., 2005; Hansen et al., 2009; Marshall et al., 2010; Schembari et al., 2014); others used monthly (Hwang and Jaakkola, 2008; Ritz et al., 2002), trimester (Padula et al., 2013; Rankin et al., 2009) or annual averages (Dolk et al., 2010), which might mask the temporal associations between air pollutants and orofacial defects. Moreover, given that teratogen exposure before pregnancy can be associated with increased risk of congenital anomalies (Shaw et al., 1999; Sun et al., 2014), the investigation of potential preconception effects of air pollution on orofacial defects is warranted but has not been addressed in previous studies.

Therefore, the objective of this study was to examine the associations of maternal exposure to criteria air pollutants [carbon monoxide (CO), nitrogen oxides (NO_x), ozone (O_3), particulate matter with aerodynamic diameter ≤ 2.5 and 10 μm ($PM_{2.5}$ and PM_{10}), and sulfur dioxide (SO_2)] with risks of orofacial defects in a large, contemporary, multi-site/region US cohort. The exposure windows of interest were three months preconception and early gestation, including both an average over weeks 3–8 of gestation to be comparable to previous studies and an exploration of individual weekly averages from weeks 1 through 10 given that the lip and palate form between weeks 5–9 of gestation (Nanci, 2012).

2. Methods

2.1. Study population and outcome

The Consortium on Safe Labor (CSL) is a retrospective cohort study of labor and delivery conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. As previously described in detail (Zhang et al., 2010), data on maternal demographic characteristics, medical history, labor, delivery, and obstetric and neonatal outcomes of 228,562 deliveries (233,736 live births and fetal deaths) at ≥ 23 weeks of gestation (January 1, 2002 to January 31, 2008) were extracted from electronic medical records. Newborn discharge diagnoses, in International Classification of Diseases-9 (ICD-9) codes, were linked to each infant. The study was approved by the institutional review boards of all participating institutions, whose names and locations can be found in the acknowledgments.

Infants with missing discharge summaries and no ICD-9 code data ($n=28{,}753$), chromosomal anomalies ($n=424$), and congenital anomalies other than orofacial defects ($n=16{,}457$) were excluded, rendering a pool of 188,102 live births and fetal deaths. Determination of orofacial defect status for each infant was obtained via ICD-9 discharge codes (see Supplemental material, Table S1). Each case without any additional major defects was classified as isolated, although there could have been minor defects as defined by the National Birth Defects Prevention Study guidelines (Rasmussen et al., 2003). Infants with orofacial defects who also had at least one other major defect either in the same or a different organ system constitute the multiple groupings.

2.2. Exposure assessment

Due to the anonymity of the CSL data, maternal ambient air pollution exposures were based on the average air pollutant concentrations in her delivery hospital referral region (415–312,644 km^2) (The Dartmouth Atlas of Health Care, 2013) during each of the specified exposure windows. A modified version of the Community Multi-scale Air Quality (CMAQ) model 4.7.1 (Foley et al., 2010) was used to estimate criteria air pollutant levels in the 15 non-overlapping hospital referral regions involved in the CSL with a 36-km horizontal resolution domain (G. Chen et al., 2014). The CMAQ simulations were based on meteorology data derived by the Weather Research and Forecasting model and emission data by National Emissions Inventories provided by the US Environmental Protection Agency (US EPA), respectively, and model results were weighted to reflect population density within the hospital referral region, discounting areas where women were unlikely to live and work.

Despite the wide use of the CMAQ model in estimating regional air quality, potential biases in meteorology and emission inputs, uncertainties of other model components, and issues with spatial resolution can compromise the precision in estimation (G. Chen et al., 2014). Thus, we used an inverse distance weighting based method to adjust raw CMAQ estimations using observational air quality data retrieved from the US EPA Air Quality System. This observation-fused technique led to significant improvement of the model performance and was demonstrated to best account for spatial variation in air pollutants and population density as compared to four other exposure estimation methods (G. Chen et al., 2014). This analysis included a three-month preconception period window, a 6-week average during organogenesis at weeks 3–8 of gestation, and weekly averages for weeks 1–10 of gestation. Gestational age in weeks was calculated from gestational age at delivery using the best obstetrical estimate as recorded in the medical record.

2.3. Statistical methods

Descriptive statistics for subject characteristics were presented as percentages for categorical variables. Differences in subject characteristics between each case group and controls were assessed by Fisher's exact test. Distributions of air pollutant concentrations were presented by quartile and interquartile range (IQR) averaged over three months preconception and weeks 3–8 of gestation. Logistic regression models were fitted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for orofacial defects per IQR increase for each air pollutant. Outcomes of interest (isolated/multiple cleft palate and cleft lip with or without cleft palate) were analyzed separately with each of the exposure windows of interest. Generalized estimating equations were used to calculate robust standard errors accounting for clustering due to multiple pregnancies of the same woman (3.9% women contributed more than one pregnancy). We selected *a priori* covariates including site/region, maternal age (<20, 20–24, 25–29, 30–34, ≥ 35 years), race/ethnicity (White, Black, Hispanic, other/unknown), marital status (married or not), insurance (private, public or other/none), prepregnancy body mass index (BMI; <18.5, 18.5–24.9, 25.0–29.9, ≥ 30.0 kg/m^2 or missing), nulliparity (yes or no), season of conception (spring, summer, fall, winter), smoking and/or alcohol consumption during pregnancy (yes or no), multiple birth (yes or no), preexisting or gestational diabetes mellitus (yes or no). Covariates were missing for $<5\%$ of the study population except prepregnancy BMI which was missing for 36.2%. We included an indicator level for missing data for categorical covariates, if necessary. Given that the CMAQ model accounts for biochemical reactions among air pollutants, effects of weather, and long-term sources of pollutants (Foley et al., 2010), air pollutants were fitted in the model separately during each exposure window of interest.

To evaluate the robustness of the findings, we performed sensitivity analyses excluding multiple gestation pregnancies and infants/fetuses born to women with preexisting or gestational diabetes, respectively. We further performed simulation extrapolation procedures (Cook and Stefanski, 1994) to correct for the potential exposure misclassification assuming a measurement error rate of