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.

Keywords

PM2.5; Ozone; Air pollution; Cleft lip; Cleft palate

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 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 weighted average. For the simple average, the county pollution estimates are averages of pollution levels of all census tracts in the county. For the population weighted average, we first calculated the weight of each county, which is the ratio of the census tract population to the county population. Then, the county average pollution estimates were calculated as the weighted average of the census tract pollution level. We used the population weighted average pollution estimates in the primary analysis, since it gave more weight to concentration levels that larger populations were exposed to. In other words, we do not know the individual addresses of the pregnant women in each county. Population weighting in principle should better represent the overall exposure of the pregnant women in a county because they are more likely to live in the population centers. When calculating the six-week average concentrations, we excluded daily $PM_{2.5}$ and ozone concentrations beyond three standard deviations for each county (less than 0.3% of daily concentrations removed for each pollutant) to avoid potential irregular air modeling behaviors.

2.3. Statistical model

We estimated prevalence ratios (PRs) of orofacial clefts by air pollution concentrations using conditional logistic regression; odds ratios from these models are mathematically equivalent to PRs. We performed logistic regression using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Two outcomes of interest were analyzed separately: CL+/-CP and CP alone. As independent variables, among variables available in the dataset, we included factors that were suspected confounders or modifiers of the association between the prevalence of orofacial clefts and air pollution, based on the literature. These covariates include infant sex, maternal race and ethnicity (classified as non-Hispanic black, non-Hispanic white, non-Hispanic other, Hispanic), maternal education (classified as 12 years or less, 13–15 years, 16 years or more), smoking status during pregnancy, mother's age, and parity (classified as nulliparous birth, when the sum of the mother's number of live births now living and number of live births now dead is zero, vs. multiparous birth, when the sum is non-zero). In addition, we included county of mother's residence as a stratification variable in the regression to control for spatial confounding and other factors related to county not captured by other variables. $PM_{2.5}$ and ozone concentrations were included in the model as linear terms, as we did not observe significant non-linear associations in exploratory data analysis.

2.4. Sensitivity analysis

To test the robustness of our results, we conducted several sensitivity analyses. First, we conducted regression analysis using county-level average concentrations based on simple averages of census tract level $PM_{2.5}$ and ozone concentrations rather than using population-weighted averages as in the primary analyses. Second, in the sensitivity analysis, we did not exclude extreme values (beyond three standard deviations) when calculating the six-week

average pollution concentrations, as we did in the primary analyses. Third, in the primary regression analyses for CL+/-CP, we included CP cases in the denominator and did the opposite for the primary CP regression analyses (i.e., included CL +/-CP cases in the denominator). In the sensitivity analysis, we tested excluding either the CP or the CL+/-CP cases from the denominator. Fourth, in the primary analysis, we assumed all births occurred on the 15th day of the birth month. In the sensitivity analysis, we assumed all births occurred one week earlier (i.e., 8th of the birth month) and one week later (i.e., 22nd of the birth month). Lastly, to explore the presence of residual confounding in our model, we tried adding exposure terms during later periods of pregnancy that, in theory, could not influence the formation of cleft lip or cleft palate, based on a slight modification of the method by Flanders et al. (Flanders, 2011). For example, we assessed whether $PM_{2.5}$ and ozone concentrations during weeks 25–30 of gestation were associated with the outcome, with $PM_{2.5}$ and ozone concentrations during weeks 5–10 already in the regression model. $PM_{2.5}$ and ozone concentrations during weeks 25–30 of gestation should not be associated with orofacial clefts after adjustment for the other variables, since an orofacial cleft will have been formed by this time. An observed significant association of $PM_{2.5}$ or ozone concentrations during weeks 25–30 with orofacial clefts would suggest residual confounding or another bias (Flanders, 2011).

3. Results

3.1. Descriptive analysis

Table 1 shows the summary of live births, live births with orofacial clefts and air pollution data from 2001 to 2007. This study has a total of nearly 4.7 million births, of which almost half were from Texas, and approximately one quarter (1.1 million births) from Florida. The overall prevalence of orofacial clefts in these four states was 15 per 10,000 live births – 9 per 10,000 with CL +/-CP and 6 per 10,000 with CP.

Table 1 shows that in the four states included in this study, the population weighted average $PM_{2.5}$ concentration of all live births during gestation weeks 5–10 was about 10 μg/m^3, with the lowest in Arizona (8.4 μg/m^3) and the highest in New York (11.2 μg/m^3). The population weighted average ozone concentration of all live births was 40.5 ppb, with the lowest in New York (~38 ppb) and the highest in Arizona (~46 ppb). We did not observe significant patterns of $PM_{2.5}$ or ozone concentrations among the different population categories, i.e., live births, all orofacial clefts, CL +/- CP, CP. The correlation between the average $PM_{2.5}$ concentration and the average ozone concentration during weeks 5–10 of gestation was 0.2. Figs. S1 and S2 in supplemental information show the population weighted average county-level $PM_{2.5}$ and ozone concentrations, respectively, in contiguous United States between 2001 and 2007. For $PM_{2.5}$, the average concentration is generally higher in the eastern United States and California. For ozone, the average concentration is generally higher in the southern part of the country. This is likely due to higher temperature and more sunlight available, which is conducive to the formation of ozone.

Table S1 summarizes study population characteristics. There were more female infants than males among CP cases, while the reverse was true for CL +/- CP and all live births (with the difference being much more pronounced for CL +/- CP than all live births). Among the four

states, Texas and Arizona had the highest proportion of Hispanic mothers (50% and 45%, respectively), while New York had the lowest (13%). Florida had the highest proportion of black, non-Hispanic mothers (21%), while Arizona had the lowest at 3%. Approximately three-quarters of the mothers in the study were between the ages of 20 and 34. About 13% of mothers from New York State smoked during pregnancy, the highest percentage among the four states. In addition, 33% of mothers from New York had at least a college degree, which was the highest among the four states. New York also had the lowest proportion of mothers with 12 years of education or less (41%). In the four states, an average of 40% of births were nulliparous births, i.e., mother's first baby.

3.2. Regression analysis

Table S2 shows odds ratios and 95% confidence intervals for potential confounders and modifiers that were adjusted for in the multivariable logistic regression analysis when data from the four states were combined. Table 2 shows the adjusted odds ratios and 95% confidence intervals for $PM_{2.5}$ and ozone based on the regression for the two outcomes of interest: CL+/-CP, and CP. $PM_{2.5}$ was positively and significantly associated with the prevalence of cleft palate alone (OR =1.43, 95% CI: 1.11–1.86) when data from the four states were combined. This means that the risk of having a baby with cleft palate alone was estimated to increase by 43% for every 10 μg/m^3 increase in county-level $PM_{2.5}$ concentration during gestational weeks 5–10, for the range of $PM_{2.5}$ concentrations considered in this study. When regression analysis were conducted for each state individually, all the odds ratio for $PM_{2.5}$ were greater than 1, meaning there was an increase in the risk of cleft palate alone with the increase in $PM_{2.5}$ concentration. However, since the sample size for each state was smaller than the four states combined, the confidence intervals were much wider. As a result, only Texas, which had the largest sample size, had the odds ratio that turned out to be significantly greater than 1 (OR =1.68, 95% CI: 1.1–2.6).

When the outcome of interest was CL+/-CP, $PM_{2.5}$ was not significantly associated with CL +/-CP, whether the four states were combined or analyzed separately. Table 2 shows that when the four states were analyzed individually, the odds ratios could be either above or below one and none of them were significantly different from one.

Ozone concentration was not statistically significantly associated with either CL+/-CP or CP, whether the four states were combined or analyzed separately. The odds ratios also had inconsistent directions from one.

3.3. Sensitivity analysis

In sensitivity analyses, we found a small difference between the population-weighted average pollutant concentrations during weeks 5– 10 of gestation and the simple average. For $PM_{2.5}$, the mean absolute difference was 0.02 μg/m^3 with a standard deviation of 0.04 μg/m^3. For ozone, the mean absolute difference was 0.04 ppb with a standard deviation of 0.07 ppb. When we used county level average concentrations based on simple averages of census tract level $PM_{2.5}$ and ozone concentrations, the direction and significance of the associations remained similar to those in Table 2, which used population weighted pollutant concentrations. Table S3 shows more details when simple averages were used. Also, when

we repeated the regression models using average $PM_{2.5}$ and ozone concentrations without removing extreme daily values beyond three standard deviations, the regression results remained similar (data not shown).

When CL+/-CP cases were the outcome of interest, we did not exclude CP cases from the denominator in the primary analysis. In the sensitivity analysis, we found that when CP cases were excluded from the denominator, there was minimal change in parameter estimates and no change in their significance. This was also true after we excluded CL+/-CP cases from the denominator when CP cases were the outcome of interest (data not shown).

When we assumed the births occurred on 8th or 22nd of the birth month, results remained similar to the primary analysis, in which the assumption was all births occurred on the 15th of the birth month. We still found that $PM_{2.5}$ significantly increased the risk of cleft palate alone, but did not increase the incidence of cleft lip with or without palate. Ozone levels did not correlate with incidence of orofacial clefts. Table S4 shows more details.

To test whether there was residual confounding, we added $PM_{2.5}$ and ozone concentrations during weeks 25–30 of gestation, in addition to $PM_{2.5}$ and ozone concentrations during weeks 5–10. Neither of the pollution terms during later periods of pregnancy was significant, suggesting no residual confounding found based on this method. Also, the parameter estimates for $PM_{2.5}$ and ozone concentrations during weeks 5–10 only changed slightly, and their significance levels remained the same as before adding the pollution terms during later periods of pregnancy (data not shown). We also found that if we did not control for county in our regression, $PM_{2.5}$ and ozone concentrations during weeks 25–30 of gestation were significantly associated with the outcome, suggesting that spatial confounding may have been present when county was not controlled for in the model.

4. Discussion

In this large population-based study, we found that maternal exposure to $PM_{2.5}$ during gestational weeks 5–10 was significantly associated with CP in the offspring. For the range of $PM_{2.5}$ concentrations considered in this study, the risk of having a baby with CP was estimated to increase by 43%, for every 10 μg/m^3 increase in county-level $PM_{2.5}$ concentration. These findings agree with another recent study (Zhu et al., 2015) that used data from 19 hospitals across the United States during a similar time period. Note that the Zhu et al. study also used the CMAQ model to estimate exposure, which is one of two inputs used in the downscaling fusion model in our current study. In contrast, studies conducted in New Jersey and Florida reported no association between $PM_{2.5}$ and CP (Marshall et al., 2010; Tanner et al., 2015), while a Texas study found no association between PM_{10} and CP (Gilboa, 2005). A meta-analysis of four studies of CP and PM_{10} also found no association (Vrijheid et al., 2011). One study conducted in Australia found a protective effect of PM_{10} on CP (Hansen et al., 2009). However, in contrast to our study, the Australian study was much smaller. It did not include $PM_{2.5}$ and used ambient air pollution data from fixed monitoring sites of PM_{10}.

We found no association between CL+/-CP and maternal $PM_{2.5}$ exposure. This result is consistent with several other studies (Marshall et al., 2010; Tanner et al., 2015; Vrijheid et al., 2011). A previous Texas study found a significantly elevated risk of CL+/-CP for maternal PM_{10} exposure during gestational weeks 3–8 (Gilboa et al., 2005). However, the Texas finding was limited to the third quartile of exposure compared with the lowest quartile; other quartiles of exposures (i.e., second, fourth) were not significant when compared with the lowest quartile.

We did not find any significant associations between orofacial clefts and maternal ozone exposure during the period of interest. This finding is consistent with most of the previous studies of ozone and orofacial clefts that we found, including two meta-analyses (Hansen et al., 2009; Ritz et al., 2002; Gilboa et al., 2005; Marshall et al., 2010; Vrijheid et al., 2011; Chen et al., 2014). However, one study conducted in Taiwan found a significantly elevated risk of CL+/-CP as ozone levels increased (Hwang and Jaakkola, 2008), although this study included PM_{10} and did not include $PM_{2.5}$ as a co-pollutant in the analysis. A recent meta-analysis (Rao et al., 2016) which included the study from Taiwan (Hwang and Jaakkola, 2008) found ozone to have the strongest correlation with cleft lip and cleft palate. However, none of the studies reviewed included $PM_{2.5}$ in the analysis.

The mechanisms by which maternal exposure to air pollutants may lead to birth defects are unknown. However, certain pollutants, including $PM_{2.5}$, are known to cross the placenta (Saenen et al., 2015) and have been found in cord blood (Herr et al., 2010). Potential mechanisms by which these pollutants could influence the risk of orofacial defects include genetic toxicity and oxidative stress. In fact, these mechanisms may interact to contribute to teratogenesis. For example, certain air pollutants (e.g., $PM_{2.5}$) could lead to genetic toxicity by forming DNA adducts (Li et al., 2014). These adducts are mutagenic, resulting in the disruption of the cell's microenvironment, which leads to inhibition of important enzymes, cell death, and alteration of other cells. If this occurs during the critical window of embryonic development, the complex cellular processes involved in development may be disturbed, leading to an oral cleft. Several air pollutants (e.g., ozone) can also form free radicals known as reactive oxygen species, which may lead to oxidative stress (Anglada et al., 2015). These reactive oxygen species can cause DNA strand breakage or fragmentation leading to cell mutation. The importance of oxidative stress as a mechanism of teratogenesis is suggested by several animal studies (Kupsco et al., 2015).

Compared with previous studies on maternal exposure to air pollution and risk for orofacial clefts, our study has several strengths. First, it has a large sample size of about 4.7 million total births and 7,000 orofacial cleft cases from four states in the United States. This is about three times the number of cases included in a study in Florida (Tanner, 2015) and at least an order of magnitude more cases than other previous analyses on this topic (Hwang and Jaakkola, 2008; Hansen, 2009; Ritz, 2002; Gilboa, 2005; Marshall et al., 2010; Zhu, 2015). In addition, except for one study (Zhu et al., 2015), previous studies in the United States used monitoring data to estimate air pollution exposure, although the spatial and temporal coverage of air pollution monitoring stations are limited. In our study, a Bayesian downscaler fusion model, which had both monitoring and modeling data as inputs, was used to estimate daily $PM_{2.5}$ and ozone concentration data ((Berrocal et al., 2012)) for the entire

contiguous United States; this model has been shown to have better performance compared with other fusion models. Furthermore, none of the previous studies on this topic assessed whether the models chosen had residual confounding, which is a challenging issue in observational studies. We added exposure terms during later periods of pregnancy that should not influence the formation of cleft lip or cleft palate. The final models used were not shown to have significant residual confounding, which provide us more confidence in the results. Lastly, the final regression models we used were robust to a series of sensitivity analyses.

Our study has a couple limitations. First, the temporal resolution for all the cases and births data are at the month level. Because we did not have access to actual birth dates, we calculated the estimated date of conception using the 15th of the birth month as the delivery date. We then took the 6-week average of $PM_{2.5}$ and ozone concentration during weeks 5–10 of gestation as our air pollution exposure variables. This limitation could result in temporal air pollution exposure mis-classification. Our sensitivity analysis showed that when we assumed the births to occur either one week earlier or one week later than the 15th of the birth month, results remained similar. Second, there are some additional misclassification of air pollution exposure. For example, we used mothers' county of residence at the time of delivery to estimate their exposures to air pollutants during weeks 5–10 of gestation. If the mother moved during their pregnancy, this could result in inaccuracies in air pollution exposure estimates. Studies showed that overall mobility rates were 9–32% and highest in the second trimester, but that most move distances were short (median often less than 10 km) (Bell and Belanger, 2012). One study in Texas showed that less than 30% of mothers moved during pregnancy and there was good agreement between quartiles of estimated benzene exposure at both addresses (Lupo, 2010).

5. Conclusion

In conclusion, our study found that ambient $PM_{2.5}$ concentrations during gestational weeks 5–10 were positively and significantly associated with risk of CP. There was a 43% increase in the risks for CP, for every 10 μg/m^3 increase in $PM_{2.5}$ concentration, for the range of $PM_{2.5}$ concentrations considered in this study. We did not observe significant association between $PM_{2.5}$ concentrations and CL+/-CP. In addition, we did not find ozone concentrations to be significantly associated with either CL+/-CP or CP. Comparing with cigarette smoking, air pollution impacts a larger population and the exposure to it is involuntary. Our results contribute to the body of evidence regarding the risk of birth defects and air pollution exposure. More work is needed to confirm this finding as well as to further explore the possible implications of our findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. EPA.

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Table 1

Summary of number of live births, live births with orofacial defects and the corresponding population weighted $PM_{2.5}$ and ozone concentration during weeks 5–10 of gestation in the study from 2001[a] to 2007[b].

State	Population	# of births	$PM_{2.5}$ concentration[c] during weeks 5–10 of gestation (μg/m³)			Ozone concentration[c] during weeks 5–10 of gestation (ppb)		
			Mean (SD)	Median (25th percentile - 75th percentile)	Min - Max	Mean (SD)	Median (25th percentile - 75th percentile)	Min - Max
AZ	Live births	553,309	8.4 (1.8)	8.1 (7.2–9.5)	3.3–13.0	45.8 (10.6)	47.4 (37.0–54.7)	24.4–66.6
	All oral clefts	953	8.4 (1.7)	8.1 (7.1–9.5)	4.1–12.7	45.8 (10.5)	47.2 (37.2–54.8)	24.4–64.9
	CL+/CP	621	8.3 (1.7)	8.0 (7.0–9.4)	4.1–12.7	46.0 (10.5)	47.8 (37.6–54.9)	24.4–64.5
	CP	332	8.5 (1.8)	8.3 (7.3–9.8)	4.4–12.7	45.5 (10.6)	47.0 (36.7–54.7)	24.5–64.9
FL	Live births	1,097,339	9.2 (1.5)	9.2 (8.1–10.2)	2.9–16.9	38.9 (7.1)	38.1 (34.1–43.7)	20.3–60.9
	All oral clefts	1462	9.2 (1.5)	9.3 (8.2–10.2)	4.4–15.0	39.3 (7.0)	38.4 (34.4–44.0)	22.1–58.3
	CL+/CP	888	9.2 (1.5)	9.3 (8.2–10.2)	4.4–15.0	39.3 (6.8)	38.5 (34.5–43.9)	22.1–57.0
	CP	574	9.3 (1.5)	9.3 (8.2–10.2)	5.2–13.2	39.2 (7.2)	38.1 (34.0–44.4)	22.5–58.3
NY[c]	Live births	754,805	11.2 (2.3)	10.9 (9.6–12.6)	4.4–21.0	37.7 (10.3)	38.1 (28.4–46.5)	15.0–64.6
	All oral clefts	1095	11.2 (2.3)	11.0 (9.5–12.5)	5.8–21.0	38.0 (10.1)	38.0 (29.1–46.8)	15.0–59.9
	CL+/CP	622	11.2 (2.3)	11.0 (9.4–12.5)	6.0–21.0	38.1 (10.1)	39.0 (28.9–46.8)	15.0–58.5
	CP	473	11.1 (2.2)	11.0 (9.6–12.5)	5.8–18.2	37.9 (10.0)	37.4 (29.2–46.7)	17.4–59.9
TX	Live births	2,292,070	10.5 (2.3)	10.4 (8.8–12.1)	3.7–19.4	40.8 (9.0)	40.6 (33.6–47.8)	21.8–69.3
	All oral clefts	3525	10.4 (2.3)	10.2 (8.6–12.0)	4.7–19.4	41.1 (9.0)	40.9 (33.7–48.0)	22.8–69.0
	CL+/CP	2295	10.3 (2.4)	10.1 (8.6–11.9)	5.0–19.4	40.9 (8.9)	40.8 (33.6–47.8)	22.8–69.0
	CP	1230	10.5 (2.3)	10.4 (8.8–12.2)	4.7–18.4	41.3 (9.1)	41.2 (33.8–48.3)	23.9–64.7
All	Live births	4,697,523	10.1 (2.3)	9.8 (8.4–11.5)	2.9–21.0	40.5 (9.3)	39.9 (33.3–47.6)	15.0–69.3
	All oral clefts	7035	10.0 (2.3)	9.8 (8.3–11.4)	4.1–21.0	40.9 (9.3)	40.3 (33.7–48.1)	15.0–69.0
	CL+/CP	4426	9.9 (2.3)	9.7 (8.3–11.3)	4.1–21.0	40.9 (9.3)	40.5 (33.8–48.0)	15.0–69.0
	CP	2609	10.1 (2.2)	9.9 (8.4–11.5)	4.4–18.4	40.7 (9.4)	40.1 (33.5–48.1)	17.4–64.9

[a] 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.

[b] All the births with week 5 of gestation on or after April 15, 2007 were excluded from the dataset to avoid including only preterm births in this analysis.

[c] NY data excluded New York City.

Table 2

Adjusted odds ratios[a] and 95% confidence intervals associated with each 10 μg/m^3 increase of PM$_{2.5}$ (μg/m^3) and 10 ppb of ozone concentrations during weeks 5–10 of gestation by state and for the four states combined, 2001[b] to 2007[c].

State	CL+/-CP[d]		CP[d]	
	OR (95% CI) for ozone	OR (95% CI) for PM2.5	OR (95% CI) for ozone	OR (95% CI) for PM2.5
Arizona	1.03 (0.94, 1.13)	1.63 (0.83, 3.23)	1.01 (0.90, 1.15)	1.53 (0.61, 3.89)
Florida	1.01 (0.90, 1.13)	0.79 (0.43, 1.46)	1.03 (0.90, 1.18)	1.00 (0.47, 2.13)
New York (excluding New York City)	1.00 (0.91, 1.09)	1.35 (0.89, 2.03)	0.95 (0.86, 1.05)	1.50 (0.94, 2.40)
Texas	1.00 (0.94, 1.06)	0.95 (0.68, 1.32)	0.97 (0.90, 1.05)	1.68 (1.08, 2.61)
Four states combined	0.99 (0.96, 1.03)	1.08 (0.88, 1.33)	0.98 (0.94, 1.03)	1.43 (1.11, 1.86)

[a]Odds ratios have been adjusted for infant sex, race-ethnicity, maternal education, smoking status during pregnancy, whether this is mother's first baby, maternal age. More details on these variables can be found in Supplementary material Table S1.

[b]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.

[c]All births with week 5 of gestation on or after April 15, 2007 were excluded from the dataset, to avoid including only preterm births in this analysis.

[d]Definition of abbreviations: CL+/-CP = cleft lip with or without cleft palate; CP =cleft palate alone; CI = confidence interval; OR = odds ratio.