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Oral Cleft Defects and Maternal Exposure to Ambient Air Pollutants in New Jersey

Elizabeth G. Marshall, Ph.D.[1], **Gerald Harris, Ph.D.**[2], and **Daniel Wartenberg, Ph.D.**[1,2]

[1]Department of Epidemiology, UMDNJ—School of Public Health, 683 Hoes Lane West, Piscataway, NJ 08854

[2]Division of Environmental Epidemiology, Department of Environmental and Occupational Medicine, UMDNJ—Robert Wood Johnson Medical School, 170 Frelinghuysen Road, Piscataway, NJ 08854

Abstract

Background—Evidence links exposure to ambient air pollution during pregnancy, particularly gaseous pollutants and particulate matter, to an increased risk of adverse reproductive outcomes but the results for birth defects have been inconsistent.

Methods—We compared estimated exposure to ambient air pollutants during early pregnancy among mothers of children with oral cleft defects (cases) to that among mothers of controls, adjusting for available risk factors from birth certificates. We obtained ambient air pollutant data from air monitoring sites in New Jersey for carbon monoxide (CO), nitrogen dioxide (NO2), ozone (O3), sulfur dioxide (SO2), particulate matter less than 10 μm in aerodynamic diameter (PM10) and particulate matter less than 2.5 μm in aerodynamic diameter (PM2.5). We used values from the nearest monitor (within 40 km of the residence at birth) for controls, cleft lip with or without cleft palate (CLP) and cleft palate only (CPO).

Results—Based on logistic regression analyses for each contaminant and all contaminants together, there were no consistent elevated associations between selected air pollutants and cleft malformations. Quartile of CO concentration showed a consistent protective association with CPO ($p<.01$). For other contaminants, confidence intervals (95%) of the odds ratios for some quartiles excluded one. CLP showed limited evidence of an association with increasing SO2 exposure while CPO showed weak associations with increasing O3 exposure.

Conclusion—There was little consistent evidence associating cleft malformations with maternal exposure to ambient air pollutants. Evaluating particular pollutants or disease subgroups would require more detailed measurement of exposure and classification of cleft defects.

Background

Recent epidemiologic studies have shown an increased risk of adverse reproductive outcomes, (e.g. low birth weight, intrauterine growth retardation, preterm birth, and neonatal mortality) with exposure to ambient air pollution during pregnancy. (Bobak and Leon, 1999; Rich et al, 2009; Ritz et al, 2000; Wilhelm and Ritz, 2003) Supported by limited toxicology and experimental evidence, (Glinianaia et al, 2004; Loder et al, 2000) accumulating evidence suggests that specific air pollutants, including particulate matter, carbon monoxide,

Corresponding Author: Elizabeth G. Marshall, Ph.D., Department of Epidemiology, UMDNJ—School of Public Health, 683 Hoes Lane West Room 210, Piscataway, NJ 08854, Voice: (732) 235-4666, Fax: (732) 235-5418, marshaeli@umdnj.edu.

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ozone, sulfur dioxide, or nitrogen dioxide, could influence pregnancy outcomes. Although the results are not as consistent as those for neonatal mortality, recent reviews conclude that there is evidence for a small adverse effect of air pollutants, particularly particulates, on fetal growth and duration of pregnancy.(Maisonet et al, 2004) Studies reporting these results have led to questions about whether exposure to air pollutants during pregnancy also could be risk factors for particular birth defects. Reviewers (Dolk and Vrijheid, 2003; Lacasana et al, 2005; Sram et al, 2005) note that there is insufficient epidemiologic evidence to evaluate the risk of air pollution and birth defects and that more research is needed. A limited number of studies have looked at specific birth defects and air pollution. (Cordier et al, 2004; Gilboa et al, 2005; Ritz et al, 2002; Strickland et al, 2009).

Oral clefts, the subject of this study, are a group of relatively common malformations that are usually divided, on the basis of the epidemiology, familial risk, and developmental sequence, into cleft lip with and without cleft palate (CLP) and cleft palate only (CPO). Both genes and environmental factors, perhaps independently or interacting, are thought to contribute to the risk of oral clefts. (Sivertsen et al, 2008; Stanier and Moore, 2004) Along with chromosomal and familial factors, there is limited evidence linking oral clefts with environmental factors experienced by the mother during pregnancy, including occupational exposures, anticonvulsants, multivitamins, alcohol, use of folic acid, and maternal smoking. (Honein et al, 2007) (Little et al, 2004) A recent study from Norway (Lie et al, 2008) showed a dose-response relationship between both passive and maternal smoking and CLP but no consistent relationship between smoking and risk of CPO.

Two studies(Gilboa et al, 2005; Ritz et al, 2002), from the western United States, evaluated the risk of birth defects (including oral clefts) associated with ambient measures of particulate matter and gaseous air pollutants, but the results were not consistent. Associations with specific heart defects were observed in both studies, and, more rarely, with oral clefts, but the two studies did not agree in the pattern of type of defects and specific pollutants. Two recent studies looked at several types of birth defects in Australia (Hansen et al, 2009)and CLP in Taiwan (Hwang and Jaakkola, 2008). Those results were also inconsistent, with only the Taiwanese study showing an association between oral clefts and level of ozone. A recent report from England showed an association between the occurrence of oral clefts and the level of black smoke and SO2. (Rankin et al, 2009). Two other studies retrospectively evaluated historic sources of combustion related to incineration of chemical wastes and lead, respectively, and showed limited evidence of an increased risk of oral clefts in regions and time periods affected by those emissions.(ten Tusscher et al, 2000; Vinceti et al, 2001).

In this study we hope to clarify previous findings by evaluating oral clefts and ambient air quality in a populous, urban and suburban northeastern state with substantial air monitoring and a population-based birth defects registry.

Methods

This study uses a case-control design to compare estimated exposure to selected ambient air pollutants during early pregnancy among mothers of children with birth defects to those for mothers of children without birth defects. Data on specific air pollutants were compiled from publicly available air monitoring data and data on cases and control characteristics were derived the birth and birth defects registries. The study did not include reviews of complete medical records or interviews of subjects.

Study Subjects

Eligible cases and controls were identified from births to New Jersey residents during 1998 to 2003, a base birth population of 690,000 births. Cases were drawn from the New Jersey Department of Health and Senior Services (NJDHSS) Special Child Health Services registry, which mandates reporting by hospitals and other health care providers of all birth defects diagnosed among live births to New Jersey residents within the first year of life. Cases for this study were those reported with a diagnosis of cleft lip with or without cleft palate (CLP) or cleft palate only (CPO). The registry identified 717 cases of CLP or CPO born between February 1998 and December 2003 and supplied identifying information, birth certificate number, diagnostic codes for all reported birth defects, and reporting source (hospital or provider identification). Oral cleft cases were excluded if they also had a diagnosis of holoprosencephaly (n = 18) since the cleft is presumed to be a consequence of a different primary defect. Cases with an additional diagnosis of a chromosome abnormality (n = 34, 2 of which also had holoprosencephaly), primarily trisomies, were excluded since the registry does not receive reports of diagnoses among terminated cases and those among live births may not be representative of all cases.

Potential controls included all births for each year from 1998–2003 (approximately 115,000 birth per year). We excluded births associated with pre-existing maternal insulin-dependent diabetes (7 cases, 2,845 potential controls) as well as those with birth weight less than 750 g (10 cases, 3,047 potential controls), plurality greater than or equal to 2 (1 case, 2,194 potential controls), maternal age less than 15 years or greater than 45 years (1 case, 2,154 potential controls), and gestational age less than 20 weeks (145 potential controls). Mothers with diabetes, extremes of maternal age, and pregnancies of plurality >2 represent unusually complex pregnancies with an increased risk of birth defects. For both cases and controls, birth records missing gestational age (both the last menstrual period and clinical estimate of gestational age) or mother's address at birth were considered ineligible. The largest group of ineligible births was those that were born to New Jersey residents in hospitals or facilities that do not supply complete electronic birth data to the state of New Jersey (approximately 2% of all New Jersey resident births), primarily those born in New York City hospitals and issued New York City birth certificates. The initial control sample was randomly chosen to include 2,500 births per year. The control sample was then matched to the New Jersey birth defects registry to exclude those with reportable birth defects (n=486).

For both cases and controls, we extracted from the birth certificate data the following variables: infant sex, maternal age, maternal education, maternal race and ethnicity, gravidity, parity, plurality, gestational age, maternal smoking during pregnancy, maternal alcohol use, month prenatal care began, marital status, access to prenatal care, insurance status, maternal diagnosis of gestational or pre-pregnancy diabetes, complications of pregnancy, maternal residential address at birth and the estimated latitude/longitude of that address.

Assignment of air pollutant measurements

The Bureau of Air Monitoring, New Jersey Department of Environmental Protection (NJ DEP) (DEP, 1998–2003) maintains ambient air monitoring sites in New Jersey for the assessment of federal and state regulated pollutants and submitted these data to the Environmental Protection Agency (EPA)to become part of the nationwide air quality system database.(EPA, 2007) The five criteria pollutants (lead in air was not considered in this study) used in this study are carbon monoxide (CO), nitrogen dioxide (NO2), ozone (O3), sulfur dioxide (SO2), particulate matter less than 10 μm in aerodynamic diameter (PM10) and particulate matter less than 2.5 μm in aerodynamic diameter (PM2.5). They are generated primarily from local and regional combustion sources (power plants, automobiles,

trucks), including the interaction of those emissions with atmospheric conditions. The air quality database provided hourly concentration (for gases) and daily average concentration (for particulate matter) from monitors located in New Jersey. Results are presented for both measures of particulate matter: those for PM10 can be compared to previous birth defects studies and those for PM2.5 as a new evaluation of an important pollutant.

The set of monitor locations used in this study are unique to each pollutant and calendar year combination. The total number, location and geographic range of monitors changed minimally during the years of the study though some monitors were discontinued, others added, and the pollutants measured changed for some, as well.(DEP) There were 43–47 total monitors per year operating from 1998–2003, with an increase in the continuous (rather than periodic) monitoring of gases, an increase in monitoring of PM2.5 over time (beginning in 1999), and a decrease in monitoring of PM10. For example, in 2002 within New Jersey there were 15 monitoring sites for CO and O3, 11 monitoring sites for NO2 and SO2, 8 monitoring sites for PM10, and 20 monitoring sites for PM2.5 (DEP) The NJ DEP supplied the latitude and longitude location of each monitor. Monitors are located primarily in urban and suburban areas to assess exposures in the most populated areas, with fewer located in rural areas. Figure 1 shows the locations of air monitoring stations in New Jersey with the birth density of each county. Data collected by the NJ DEP follow EPA requirements for participation in the nationwide Air Quality System including specific methods used to measure particulates, quality assurance/quality control data collection standards, and reporting requirements.(EPA, 2007)

To estimate exposure, we matched maternal residence at birth recorded on the birth certificate to the closest routine air pollutant monitor(s). Since the 1998 birth year, maternal residence at birth as recorded on the New Jersey birth certificate has been geocoded routinely to the closest matching address. For 1999–2003 births, the matching process was carried out under contract with Geographic Data Technology, Inc. (GDT, Inc., Lebanon, NH) using standard geographic information systems automated processes to match the input address with source maps from the United States Census and GDT. For 1998, geocoding was conducted by the NJDHSS using a similar process along with some manual matching (K. Hempstead, NJDHSS, personal communication). For 1999–2003, each address that could not be matched to an exact address was, whenever possible, assigned a centroid location for zip + 4, zip +2, or zip code polygons. For the purposes of this project, any address that could not be matched to at least a zip code +2 was excluded. Among all eligible cases and controls, 97.8% were assigned a latitude and longitude for residence at birth. There were no differences in the proportion successfully geocoded between cases and controls.

Monitor locations were combined with residence at birth addresses to estimate the distance from each monitor to each residence at birth in the study. For the primary hypothesis-testing analysis, the air monitoring station closest to the residence at birth for each case and control served as the estimate of exposure for that birth. All births within 40 kilometers (25 miles) of at least one monitoring station were included in most analyses. This distance balanced the inclusion of most subject residences with how well exposure estimates generated from these monitors represented nearby residential areas. To assess the effects of misclassification of exposure, we repeated the major analyses including only those residences at birth within 10 km of an ambient air monitor.

Case and control residences at birth not within 40km of an ambient air monitoring station ranged from 1%–5% for O3, SO2, NO2, PM2.5, and CO, and from 12%–16% for PM10. To evaluate the effect of potential misclassification of exposure due to distance from the nearest monitor, analyses were repeated using the primary models but restricting subject residences

to those within 10km of the applicable monitor. This resulted in fewer cases and controls in these regression analyses. The mean distances to monitors varied by contaminant and by year. For example, in 1998, the mean distance from a residence to an O3 monitor (most monitors) was 12.9 km and 13.0 km for cases and controls, respectively. For NO2 in 1998 (fewest monitors), the mean distance was 20.7 km for cases and 20.1 km for controls.

Using date of birth and gestational age, an estimated date of conception was generated for each case and control. Gestational age was calculated as the number of complete weeks between the date of the mother's last menstrual period as reported on the birth certificate and the date of birth (Engle, 2004). If the date of the last menstrual period was missing or resulted in a gestational age outside of the appropriate range, the estimated clinical gestational age was used to generate a conception date. The critical exposure period was defined as a 6 week period from 5 to 10 weeks into the gestational period with the start of the gestational period defined as the date of birth minus the gestational age, corresponding to the timeframe of structural development and the greatest period of vulnerability for the risk of birth defects.(Tolarova and Cervenka, 1998) Since exposure data were only available beginning with January 1, 1998, births eligible to be included in the analyses required a period of vulnerability beginning on or after that date.

For each contaminant, a mean concentration was computed for the 6 week period based on continuous or periodic monitoring for that contaminant, averaging values recorded within those weeks. We also assessed the importance of peak values, by assigning subject residences the number of days within the critical period that the air pollutant exceeded the 90^{th} percentile for that pollutant. These numbers were compared between cases and controls. The effect of missing monitoring data was evaluated separately for each contaminant. In most cases, monitoring data is missing for a few hours or sometimes days and was unlikely to affect the overall mean exposure during the critical exposure period. Using the protocol defined by Gilboa et al.(Gilboa et al, 2005), at least 70% of values for the applicable time period were required to be available for that residence's monitoring data to be included. If not, that residence was excluded for that analysis unless there was another monitor within the chosen distance radius and the data were available. The percentage excluded because of missing data differed by year and the contaminants measured. For SO2, O3, NO2, CO, and PM10 the percent missing applicable contaminant monitoring values ranged from 0.2% to 2.1% for controls, 1.7% to 3.9% for CLP, and 0% to 1.3% for CPO. Consistent monitoring for PM2.5 did not occur until 1999. For 1999–2003 study births PM2.5 was missing for 1.7% to 4.1%.

Data Analysis

We conducted initial descriptive analyses to identify outlying and missing values, and to demonstrate the general geographic distributions of air pollutant exposure and residences of cases and controls. Further analyses compared the distribution of potential confounders and season of conception among cases and controls. Risk factors known to be associated with oral cleft risk in previous studies were maintained in the models, including mother's age, race, ethnicity, smoking and drinking alcohol during pregnancy, and season of conception. We evaluated smoking for potential effect modification by stratification and by inclusion of an interaction term in the summary models.

Logistic regression analyses were conducted separately for each contaminant and cleft subgroup combination. Exposure to each air pollutant was included as the quartile of exposure, calculated using the distribution among controls. The lowest quartile served as the reference group. In addition to performing the logistic regression analyses by breaking the exposure concentrations into 4 groups, we also performed analyses on the original continuous data using a linear and quadratic term for each pollutant concentration. Each

pollutant concentration distribution was standardized to have mean zero and standard deviation one. To produce Figures 2–3, the control births were divided into 20 exposure groups so that each group would have approximately the same number of observations. The proportion of cases within each exposure group was plotted against the average pollutant concentration within each total exposure group. Vertical lines about the mean indicate approximate 95% confidence intervals. Trend lines in Figures 2 and 3 were computed using a Loess smoother.

We also conducted analyses to assess the effect of multiple pollutant exposures on clefts. Multiple pollutant effects were evaluated in two ways: 1) by simultaneously entering all 6 pollutant concentrations into the logistic regression model (along with the potential confounders previously identified), and 2) by selecting pollutants in a stepwise fashion (P-to-enter = 0.15; P-to-remove = 0.20) in the logistic regression model after accounting for confounders. Evaluating multiple contaminants simultaneously reduces the available sample by approximately 40% over the single contaminant analyses because all 6 pollutants must be available for each residence location to be included.

Results

Table 1 shows the attributes of all eligible cases and controls. For CLP, cases were more likely to be male, and to have mothers with less education and white or Hispanic ethnicity. They were more likely to report smoking and drinking during pregnancy. For CPO compared to controls, cases were more likely to be girls or to have mothers of white ethnicity and somewhat older ages. Smoking but not drinking was associated with CPO. There was no apparent relationship between the risk of either disease group and gravidity or season of conception.

Mean values for all contaminants (Table 2) showed little difference among the control and two case groups. In terms of acute exposure to high levels of ambient air pollution, the proportion of daily values greater than the ninetieth percentile were similar for all contaminants among cases and controls.

Table 3 summarizes the results of logistic regression analyses from each single pollutant model, adjusting for mother’s age, education, race/ethnicity, gravidity, alcohol and smoking during pregnancy, and infant sex. Only one model showed a statistically significant association with the overall indicator for quartile concentration in the logistic regression model (CO concentration showed a protective association with CPO ($p<0.01$)); all other pollutants were not statistically significant for the overall association with disease status (data not shown). Odds ratios for each quartile of average pollutant concentration during the critical period are presented with the lowest quartile as the referent group. There are few odds ratios consistently different from 1.0 for any single pollutant. However, confidence intervals for some odds ratios excluded one, but only for a few quartiles. Most notably, CLP showed some evidence of a positive association with SO2 exposure including a statistically significant elevated risk at the highest quartile of exposure. CPO showed a weak positive association with ozone exposure and a weak protective association with CO exposure. For the latter, the confidence interval was below 1.0 for the highest quartile. There was no evidence of effect modification by smoking.

The logistic regression results by quartile are mirrored in Figures 2 and 3 which graphically present the relationship between monitoring values and risk of CLP and CPO. There is little evidence of clear dose response relationships. Several contaminants (SO2, CO, NO2) show a weak pattern of decreasing risk of CPO with increasing concentration while O3 and PM2.5 indicate slight increasing risk with increasing concentration.

Table 4 evaluates the effect of narrowing the geographic spread of monitors to apply only to residences within 10km of the closest monitor. This drastically reduced the number of eligible cases and controls but the results, in terms of point estimates, are not substantially different. Only the association between O3 and CPO showed generally increased odds ratios in comparison to those measured using monitors within 40km, which might be expected with increasing accuracy of exposure measurement.

Our results did not change substantially when we considered multiple pollutants. We found that increasing CO concentration was associated with a protective effect on CPO even after accounting for other pollutants. To assess whether these results might differ since they were based on a subset of resident locations with all six pollutant concentrations available, we fit the single pollutant logistic regressions using the subset sample. These results were similar to those found using the entire sample by individual pollutant. They also indicated only the protective association between CO and CPO and similar weak associations with SO2 and O3 (results not shown).

When the pollutant concentrations were characterized by the raw continuous data (rather than categorized into quartiles), we found a negative linear relationship between CO and CPO, weak positive linear relationships between PM10 and CPO and between SO2 and CLP, and a negative quadratic relationship between Ozone and CPO. These results are similar to those found using a categorized pollutant concentration. These associations are reflected in the plots shown in Figures 2–3.

Discussion

This study estimated maternal residential exposure to specific markers of ambient air pollutants in New Jersey and evaluated the risk of two subgroups of oral cleft birth defects based on geographic location. The analysis confirmed previously known risk factors for cleft defects, including infant sex, maternal race, and smoking during pregnancy, but there was little evidence of increased risks of oral clefts associated with the estimated concentration of six ambient air pollutants (PM2.5, PM10, SO2, NO2, O3, and CO). There was a consistent protective relationship between CO measured at both <40km and <10km and the risk of CPO, even after controlling for socioeconomic and demographic variables. This result is difficult to interpret or attribute to confounding by other sociodemographic factors or environmental exposures. Other results that merit further evaluation include evidence for an increased risk of CLP with SO2 exposure and an association between O3 and CPO.

These results add to the limited evidence relating oral clefts and ambient air pollution. In two previous United States case-control studies from Southern California (Ritz et al, 2002) and Texas (Gilboa et al, 2005), investigators showed only weak associations with similar exposure estimates. The first study (Ritz et al, 2002) did not find a significant relationship between the risk of oral clefts and any of the pollutants measured, though there was an inconsistent elevation in risk related to carbon monoxide. The second (Gilboa et al, 2005) found a limited association (odds ratios 1.29–1.45) between isolated CLP and increasing PM10, though it was statistically significant for only the second quartile of exposure. Associations between isolated CLP and other pollutants were not consistently elevated and the results for CPO were inconsistent for all pollutants. In our analyses, there was only a slightly increased risk of CLP associated with PM2.5 or PM10 by quartile (odds ratios from 1.2–1.3); they were not statistically significant and showed no dose-response relationship. Two recent studies outside the United States (Australia and Taiwan) included only CLP. Hwang and Jaakkola (2008) showed a significant association between CLP and ozone, while Hansen et al (2009) showed a weak association between CLP and SO2. Only the latter was evident in our results shown here. Like the current study, these studies relied on registry

ascertainment, birth certificate data on residence at birth, and ambient air monitoring results. Although California, Texas, and New Jersey have quite different weather, geographic features and patterns of air pollution, the actual levels of pollutants by concentration were similar, except for carbon monoxide, which was somewhat higher in California. Our analysis is the first analysis of birth defects to examine the effects of PM2.5, which has more recently been a focus of monitoring instead of PM10, because the smaller particles are presumed to be more toxic. There was no evidence of an association in this study between oral cleft defects and levels of PM2.5.

This study confirmed the feasibility of geographically linking birth certificates, birth defect registry data, and ambient air monitoring data for analytic studies. All these data sources are accessible to many state monitoring systems, including those with birth defects registries that rely on reports from health care providers rather than active ascertainment of cases. New Jersey is densely populated and primarily urban and suburban, increasing the chances of accurate and automated geocoding of residential location. Like many statewide monitoring systems, we dealt with missing and incomplete data for some birth certificates because of border issues and incomplete data. However, there was evidence that despite these limitations, we replicated elevated risk factors shown in interview studies with more detailed collection of data. We successfully linked the majority of residence locations to air monitoring stations and generated a specific concentration measure based on time and space. Despite problems in estimating exposure using previously collected environmental data for broad geographic areas, these methods provide a model that could be applied to environmental health surveillance of birth defects.

Unlike some defects (such as some heart defects) oral cleft defects fit reasonably well within the ICD-9 coding available to us and used in reporting birth defects by health care providers. This is in contrast to the more detailed coding used by registries and studies with complete review of medical records, which is far more expensive and labor intensive. (Rasmussen et al, 2003) We made every effort to examine CLP and CPO of similar derivation separately: those with a defect that might clearly cause oral clefts were excluded and those with known chromosome abnormalities were excluded. Even so, we were unable to assess which CLP and CPO cases were isolated and which had multi-system defects because of the limitations of coding and lack of detailed medical records. We also had no data on which cases and controls had a family history of oral cleft defects. Previous studies based on extensive medical record review and classification indicate that around 70%–88% of these defects are isolated, depending on the population and criteria used (Shaw et al, 2006; Sivertsen et al, 2008). However, the inclusion of infants with isolated and multiple defects together is a limitation of this study

There were several sources of measurement error in the estimation of ambient air pollutant levels and the amount of error likely varied by contaminant. The limitations in the exposure assessment methods are similar to those facing other geographic studies of reproductive outcomes and air pollution (Woodruff et al, 2009). Ambient air monitoring stations cover a wide variety of locations and contaminants and the contaminants measured at each monitor differed over time. This study assumes all monitors within 40km of a residence at birth are equally representative of the air at that location, which may not be valid. In some cases, such as particulate matter in the Northeastern United States, the results represent values that are similar across a wide geographic area because of regional transport of pollutants. Thus, the variation in pollutant values for particulates derives from variation across time and season in addition to some differences within the state. Ozone varies drastically by season and much less by geographic area. Carbon monoxide is known to vary substantially across small distances and to depend on local conditions. CO monitors were more likely to be classified

as having a smaller spatial scale compared to other pollutants. Thus for CO, there is likely to be more misclassification, especially when including all residences within 40 km.

Birth defects represent rare birth outcomes and we included all residences within 40km of a monitor to include as many as possible while still applying a valid measurement of ambient air pollution. We compared the results for 40km to those within 10km to make some assessment of the influence of distance and found few differences in the results but the exposure measurements are inexact. Besides misclassification due to the distance between monitoring stations and residences, a substantial proportion of the geographic locations identified as the residence at birth are not the actual residence during early pregnancy when oral clefts develop. Previous studies have shown that 25%–30% of mothers move during pregnancy (Canfield et al, 2006). Many of these moves, if close by, might not substantially alter the exposure estimates, but the actual level of misclassification is unknown. We also had no data on the actual time mothers spent at their residence, or information on other indoor air, workplace, or medical exposures that occurred during pregnancy.

Our study showed little evidence of an increased risk of oral clefts defects with exposure to ambient air pollutants during 1998–2003. Because of limitations of the exposure assessment process and classification of birth defects, we cannot rule out an increased risk associated with particular pollutants or disease subgroups. These results differ from those evaluating other adverse reproductive outcomes, such as low birth weight and premature birth, which have shown more consistent risks associated with specific air pollutants, especially particulate matter. However, it is more difficult to conclusively measure the effects of the exposure because birth defects occur much less frequently. To gain more definitive results, future studies should use more exact exposure characterization, interviews to assess potential confounders more completely, and evaluate distribution over space and time in more detail.

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Figure 1.
Distribution of births and air monitoring locations in New Jersey by county

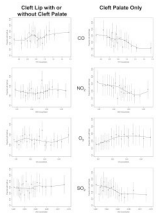

Figure 2.
Comparison of proportion of cases by air pollutant (gases) concentration. Vertical lines about the mean indicate approximate 95% confidence intervals. Trend lines were computed using a Loess smoother.

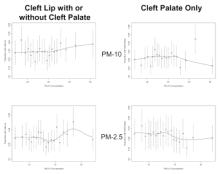

Figure 3.
Comparison of proportion of cases by air pollutant (particulate matter) concentration. Vertical lines about the mean indicate approximate 95% confidence intervals. Trend lines were computed using a Loess smoother.

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Table 1

Characteristics of cases and controls, including all eligible subjects.

	Controls (N = 12,925)		Cleft lip (N = 414)			Cleft Palate Only (N = 303)		
Variable	**N[a]**	**%**	**N[a]**	**%**	**OR (95% CI)**	**N[a]**	**%**	**OR (95% CI)**
Baby's sex								
Male	6,518	50.4	261	63.0	1.7 (1.4 – 2.1)	134	44.2	0.8 (0.6 – 1.0)
Female	6,407	49.6	153	37.0	1.0	169	55.8	1.0
Mother's Education								
<HS	1,745	13.8	71	17.9	1.4 (1.1 – 1.8)	33	11.2	0.8 (0.5 – 1.2)
HS	3,673	29.1	116	29.3	1.1 (0.9 – 1.4)	90	30.6	1.0 (0.8 – 1.3)
College +	7,197	57.1	209	52.8	1.0	171	58.2	1.0
Mother's Race/Ethnicity								
NH White	6,944	53.9	227	55.0	1.0	187	61.9	1.0
NH Black	2,069	16.1	46	11.1	0.7 (0.5 – 0.9)	41	13.6	0.7 (0.5 – 1.0)
Hispanic	2,777	21.5	104	25.2	1.1 (0.9 – 1.5)	51	16.9	0.7 (0.5 – 0.9)
Other	1,100	8.5	36	8.7	1.0 (0.7 – 1.4)	23	7.6	0.8 (0.5 – 1.2)
Smoking during Pregnancy								
No	11,689	91.6	358	87.3	1.0	266	88.4	1.0
1–14 cig/day	853	6.7	42	10.2	1.6 (1.2 – 2.2)	25	8.3	1.3 (0.8 – 2.0)
15+ cig/day	216	1.7	10	2.4	1.5 (0.8 – 2.9)	10	3.3	2.0 (1.1 – 3.9)
Gravidity								
Multigravid	7,638	59.1	241	58.2	1.0	168	55.6	1.0
Primigravid	5,275	40.9	173	41.8	1.0 (0.9 – 1.3)	134	44.4	1.2 (0.9 – 1.5)
Mother's Age								
15–20	926	7.2	34	8.2	1.2 (0.8 – 1.8)	16	5.3	0.8 (0.5 – 1.3)
21–25	2,204	17.1	75	18.1	1.1 (0.8 – 1.5)	54	17.8	1.1 (0.8 – 1.5)
26–30	3,204	24.8	105	25.4	1.1 (0.8 – 1.4)	65	21.5	0.9 (0.7 – 1.3)
31–35	3,995	30.9	122	29.5	1.0	89	29.4	1.0
36–40	2,164	16.7	63	15.2	1.0 (0.7 – 1.3)	68	22.4	1.4 (1.0 – 1.9)
41–45	432	3.3	15	3.6	1.1 (0.7 – 2.0)	11	3.6	1.1 (0.6 – 2.2)

Variable	Controls (N = 12,925)		Cleft lip (N = 414)			Cleft Palate Only (N = 303)		
	N[a]	%	N[a]	%	OR (95% CI)	N[a]	%	OR (95% CI)
Drinker								
No	12,696	98.8	398	96.8	1.0	297	98.7	1.0
Yes	159	1.2	13	3.2	2.6 (1.5 – 4.6)	4	1.3	1.1 (0.4 – 2.9)
Season of Conception								
Winter	3,599	27.8	121	29.2	1.0	87	28.7	1.0
Spring	2,984	23.1	85	20.5	0.8 (0.6 – 1.1)	84	27.7	1.2 (0.9 – 1.6)
Summer	3,039	23.5	112	27.1	1.1 (0.8 – 1.4)	70	23.1	1.0 (0.7 – 1.3)
Autumn	3,303	25.6	96	23.2	0.9 (0.7 – 1.1)	62	20.5	0.8 (0.6 – 1.1)

[a]Number of observations within each variable may not add to total at top of column due to missing values.

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Table 2

Estimated exposure to ambient air pollutants at residence at birth for oral cleft cases and controls during the critical period of pregnancy.

	Controls N = 12,925	CLP N = 414	CPO N = 303
PM2.5			
% missing (N)	20.7 (2,673)	21.7 (90)	18.8 (57)
Mean (StdDev) (μg/m^3)	13.4 (3.6)	13.6 (3.7)	13.2 (3.6)
%>90th percentile (SD)	9.8 (9.8)	10.8 (10.8)	9.9 (10.2)
PM10			
% missing (N)	1.4 (183)	3.9 (16)	1.3 (4)
Mean (StdDev) (μg/m^3)	28.1 (8.9)	28.7 (9.3)	28.0 (8.6)
%>90th percentile (SD)	10.5 (13.6)	10.6 (14.2)	10.4 (13.7)
NO2			
% missing (N)	0.2 (27)	1.7 (7)	0 (0)
Mean (StdDev) (ppm)	2.4E-2 (0.8E-2)	2.4E-2 (0.8E-2)	2.2E-2 (0.8E-2)
%>90th percentile (SD)	10.6 (15.7)	11.4 (16.0)	8.4 (14.9)
SO2			
% missing (N)	0.2 (27)	1.7 (7)	0 (0)
Mean (StdDev) (ppm)	5.1E-3 (2.2E-3)	5.3E-3 (2.4E-3)	4.8E-3 (2.1E-3)
%>90th percentile (SD)	9.8 (13.0)	10.7 (14.5)	7.7 (11.9)
O3			
% missing (N)	2.1 (276)	4.1 (17)	1.3 (4)
Mean (StdDev) (ppm)	2.5E-2 (1.1E-2)	2.5E-2 (1.1E-2)	2.6E-2 (1.0E-2)
%>90th percentile (SD)	7.6 (13.3)	7.9 (13.9)	8.8 (13.9)
CO			
% missing (N)	0.6 (78)	1.7 (7)	0.3 (1)
Mean (StdDev) (ppm)	0.83 (0.31)	0.85 (0.32)	0.74 (0.28)
%>90th percentile (SD)	7.7 (13.1)	8.7 (14.5)	4.7 (10.7)

Table 3

Adjusted[a] odds ratios and 95% confidence intervals for cleft lip and cleft palate associated with quartiles of average concentration during weeks 3–8 of pregnancy for individual air pollutants. All residences within 40 km of the closest air monitoring station are included.

	Cleft lip +/− cleft palate		Cleft Palate only	
	N	OR (95% CI)	N	OR (95% CI)
PM2.5(μg/m^3)				
<20	61	1	62	1
20–25	74	1.2 (0.8 – 1.7)	56	0.9 (0.6 – 1.3)
25–30	75	1.2 (0.8 – 1.7)	53	0.8 (0.6 – 1.2)
>30	82	1.3 (0.9 – 1.8)	51	0.8 (0.6 – 1.2)
PM10 (μg/m^3)				
<22.0	79	1	49	1
22.0–27.5	72	0.9 (0.6 – 1.2)	66	1.3 (0.9 – 1.9)
27.5–33.5	68	0.8 (0.6 – 1.2)	64	1.3 (0.9 – 1.9)
>33.5	92	1.1 (0.8 – 1.5)	62	1.2 (0.8 – 1.8)
NO2(ppm)				
<.02	73	1	79	1
.018–.024	75	1.1 (0.8 – 1.5)	64	0.9 (0.6 – 1.3)
.024–.030	82	1.2 (0.9 – 1.7)	55	0.8 (0.5 – 1.1)
>.030	90	1.3 (0.9 – 1.8)	45	0.6 (0.4 – 1.0)
SO2(ppm)				
<.003	79	1	76	1
.003-.005	89	1.2 (0.9 – 1.7)	84	1.2 (0.8 – 1.6)
.005–.007	88	1.3 (0.9 – 1.9)	67	1.0 (0.7 – 1.4)
>.007	96	1.6 (1.1 – 2.2)	49	0.7 (0.5 – 1.1)
Ozone(ppm)				
<.015	90	1	54	1
.015–.023	101	1.0 (0.7 – 1.4)	72	1.3 (0.9 – 1.9)
.023–.033	99	1.0 (0.7 – 1.4)	80	1.4 (0.9 – 2.3)
>.033	86	0.9 (0.6 – 1.3)	80	1.4 (0.9 – 2.3)
CO(ppm)				
<.65	83	1	89	1
0.65–0.80	94	1.2 (0.9 – 1.6)	74	0.9 (0.6 – 1.2)
0.80–1.02	82	1.1 (0.8 – 1.5)	71	0.9 (0.6 – 1.2)
>1.02	105	1.4 (1.0 – 1.9)	40	0.5 (0.3 – 0.7)

[a]Results adjusted for mother's race, age, education, gravidity, alcohol use, and smoking, season of conception, and infant sex.

Table 4

Adjusted[a] odds ratios and 95% confidence intervals for cleft lip and cleft palate associated with quartiles of average concentration during weeks 3–8 of pregnancy for individual air pollutants. All residences within 10 km of the closest air monitoring station are included.

	Cleft lip +/− cleft palate		Cleft Palate only	
	N	**OR (95% CI)**	**N**	**OR (95% CI)**
PM2.5 ($\mu g/m^3$)				
<20	30	1	25	1
20–25	41	1.0 (0.6 – 1.7)	34	1.2 (0.7 – 2.0)
25–30	39	0.9 (0.5 – 1.5)	28	0.9 (0.5 – 1.6)
>30	61	1.3 (0.8 – 2.0)	32	1.0 (0.6 – 1.7)
PM10 ($\mu g/m^3$)				
<22.0	24	1	20	1
22.0–27.5	40	1.3 (0.8 – 2.2)	23	0.9 (0.5 – 1.8)
27.5–33.5	32	0.9 (0.5 – 1.6)	24	0.8 (0.4 – 1.5)
>33.5	47	1.4 (0.8 – 2.3)	20	0.7 (0.4 – 1.4)
NO2(ppm)				
<.02	31	1	21	1
.018–.024	27	0.7 (0.4 – 1.2)	29	1.2 (0.7 – 2.2)
.024–.030	44	0.9 (0.6 – 1.5)	25	0.8 (0.4 – 1.4)
>.030	54	1.0 (0.6 – 1.6)	21	0.5 (0.3 – 1.0)
SO2(ppm)				
<.003	27	1	23	1
.003–.005	28	1.0 (0.6 – 1.8)	22	0.8 (0.4 – 1.4)
.005–.007	54	1.5 (0.9 – 2.5)	32	0.8 (0.5 – 1.5)
>.007	57	1.4 (0.8 – 2.3)	29	0.6 (0.3 – 1.1)
Ozone(ppm)				
<.015	45	1	24	1
.015–.023	53	1.3 (0.8 – 2.2)	31	1.7 (0.9 – 3.2)
.023–.033	50	1.2 (0.7 – 2.2)	37	2.1 (1.0 – 4.3)
>.033	29	1.0 (0.5 – 1.9)	26	2.2 (1.0 – 4.9)
CO(ppm)				
<.65	36	1	36	1
0.65–0.80	42	1.1 (0.7 – 1.7)	29	0.8 (0.5 – 1.3)
0.80–1.02	35	0.9 (0.5 – 1.4)	28	0.7 (0.4 – 1.2)
>1.02	71	1.3 (0.8 – 1.9)	21	0.4 (0.2 – 0.7)

[a]Results adjusted for mother's race, age, education, gravidity, alcohol use, and smoking, season of conception, and infant sex.