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Traffic-Related Air Pollution and Selected Birth Defects in the San Joaquin Valley of California

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Abstract

BACKGROUND—Birth defects are a leading cause of infant morbidity and mortality. Studies suggest associations between environmental contaminants and some structural anomalies, although evidence is limited and several anomalies have not been investigated previously.

METHODS—We used data from the California Center of the National Birth Defects Prevention Study and the Children's Health and Air Pollution Study to estimate the odds of 26 congenital birth defect phenotypes with respect to quartiles of seven ambient air pollutant and traffic exposures in California during the first 2 months of pregnancy, 1997 to 2006 (874 cases and 849 controls). We calculated odds ratios (adjusted for maternal race/ethnicity, education, and vitamin use; aOR) for 11 phenotypes that had at least 40 cases.

RESULTS—Few odds ratios had confidence intervals that did not include 1.0. Odds of esophageal atresia were increased for the highest versus lowest of traffic density (aOR = 2.8, 95% confidence interval [CI], 1.1–7.4) and PM_{10} exposure (aOR 4.9; 95% CI, 1.4–17.2). PM_{10} was associated with a decreased risk of hydrocephaly (aOR= 0.3; 95% CI, 0.1–0.9) and CO with decreased risk of anotia/microtia (aOR = 0.4; 95% CI, 0.2–0.8) and transverse limb deficiency (aOR = 0.4; 95% CI, 0.2–0.9), again reflecting highest versus lowest quartile comparisons.

CONCLUSION—Most analyses showed no substantive association between air pollution and the selected birth defects with few exceptions of mixed results.

Keywords

congenital anomalies; air pollution; traffic; birth outcomes

INTRODUCTION

Birth defects are a leading cause of infant mortality and an important contributor to childhood and adult morbidity. Major structural birth defects are diagnosed in 2 to 4% of

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infants (Canfield et al., 2006). Although some can be attributed to chromosomal abnormalities or known teratogenic agents, the etiologies of most cases remain unknown. Environmental contaminants have been suggested as risk factors for some anomaly groups; however, few studies have investigated the full spectrum of major structural birth defects in specific phenotypic groupings (Rankin et al., 2009; Dolk et al., 2010).

Epidemiologic studies of the past decade have identified associations between air pollution and adverse birth outcomes, including low birth weight, preterm birth, and infant mortality (Glinianaia et al., 2004; Maisonet et al., 2004; Sram et al., 2005). Studies focusing on birth defects (Ritz et al., 2002; Gilboa et al., 2005; Kim et al., 2007; Hwang et al., 2008; Hansen et al., 2009; Rankin et al., 2009; Strickland et al., 2009; Marshall and Lock, 2010; Marshall et al., 2010; Dolk et al., 2010; Ritz, 2010; Dadvand et al., 2010, 2011; Forastiere et al., 2011; Li et al., 2011; Lupo et al., 2011) and their potential relation with air pollutants have not produced clear results (Vrijheid et al., 2011). Many studies have been limited to residential information at birth rather than early in pregnancy, a known critical exposure period for birth defects. Only one previous study has incorporated data on traffic exposure (Dadvand et al., 2011). A recent systematic review suggested future studies address the following advances: (1) more precise spatiotemporal models of exposure with a focus on traffic-related pollutants; (2) careful classification of cases; and (3) focused investigation of anomalies for which there may be an environmental etiology (Vrijheid et al., 2011).

In two previous analyses we examined associations between traffic-related air pollution and neural tube defects, orofacial clefts, gastroschisis (Padula et al., 2013a), and several congenital heart defects (Padula et al., 2013b) with data from the California Center of the National Birth Defects Prevention Study (Yoon et al., 2001) and the Children's Health and Air Pollution Study. The aim of the current analysis was to investigate whether ambient air pollution and traffic metrics contributed to the risks of other structural anomalies in the San Joaquin Valley of California. The current study provides thorough case ascertainment and classification in a population-based case-control study with detailed exposure assessment in a region of the United States with poor air quality.

METHODS

Study Population

The California Center of the National Birth Defects Prevention Study is a collaborative partnership between Stanford University and the California Birth Defects Monitoring Program in the Department of Public Health. Since 1997, the Center has been collecting data from women residing in eight counties (San Joaquin, Stanislaus, Merced, Madera, Fresno, Kings, Tulare, and Kern) in the San Joaquin Valley. The California Birth Defects Monitoring Program is a well-known surveillance program that is population-based (Croen et al., 1991). To identify cases with birth defects, data collection staff visit all hospitals with obstetric or pediatric services, cytogenetic laboratories, and all clinical genetics prenatal and postnatal outpatient services.

Cases in the current analysis included infants or fetuses with birth defects confirmed by clinical, surgical, or autopsy reports. Cases resulting from known single gene or

chromosomal abnormalities or with identifiable syndromes were ineligible, given their presumed distinct underlying etiology. Eligible cases included live births, stillbirths, and pregnancy terminations.

Controls included nonmalformed live-born infants randomly selected from birth hospitals to represent the population from which the cases arise (approximately 150 per study year). Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between 6 weeks and 24 months after the infant's estimated date of delivery. Estimated date of conception was derived by subtracting 266 days from expected date of delivery. Expected date of delivery was based on self-report; if unknown, it was estimated from information in the medical record (<2% of participants) (Yoon et al., 2001). Interviews were conducted with mothers of 70% of eligible cases and 69% of controls. Mothers reported a full residential history from 3 month before conception through delivery, including dates occupying each residence. Addresses were geocoded using the Centrus Desktop (Stamford, CT), which combines reference street networks from Tele Atlas (′s-Hertogenbosch, Netherlands) and United States Postal Service data. Geocodes were available for 95% of cases and 93% of controls. Mothers with diabetes (Type 1 or 2) before gestation were excluded from analyses.

Case phenotypes for analysis included: anotia/microtia (*n* = 106), anorectal atresia/stenosis (*n* = 91), craniosynos tosis (*n* = 87), hypospadias second or third degree (*n* = 67), diaphragmatic hernia (*n* = 66), transverse limb deficiency (*n* = 63), intestinal atresia/stenosis (*n* = 52), amniotic band syndrome and limb body wall complex (ABS-LBWC) (*n* = 49), hydrocephaly (*n* = 46), longitudinal limb deficiency (*n* = 45), esophageal atresia (*n* = 44), and 853 controls with an estimated delivery date between October 1, 1997 and December 31, 2006. Birth defects with less than 40 cases were analyzed but not presented due to insufficient power. These defects included omphalocele (*n* = 38), bilateral renal agenesis or hypoplasia (*n* = 24), Dandy-Walker malformation (n 516), duodenal atresia/stenosis (*n* = 16), cataracts (*n* = 15), anophthalmos/microphthalmos (*n* = 15), holoprosencephaly (*n* = 14), biliary atresia (*n* = 14), colonic atresia/stenosis (*n* = 9), cloacal exstrophy (*n* = 8), sacral agenesis or caudal dysplasia (n 58), glaucoma/anterior chamber defects (*n* = 7), choanal atresia (*n* = 7), bladder exstrophy (*n* = 6), cerebellar hypoplasia (*n* = 3).

Exposure Assessment

As part of the Children's Health and Air Pollution Study, ambient air pollution measurements and traffic metrics were assigned to each of the geocoded residences reported by study subjects corresponding to their first and second month of pregnancy. If there was more than one address during the first or second months, exposure assignments were calculated for number of days at each residence. Exposure assignments were made if the geocodes were within the San Joaquin Valley and the mother resided there for at least 75% of each month. Daily 24-hr averages were averaged over the first 2 months of pregnancy for the following pollutants: nitrogen dioxide (NO_2), nitrogen oxide (NO), carbon monoxide (CO), particulate matter with aerodynamic diameter ≤than 10 μm (PM_{10}), and PM ≤ than 2.5 μm ($PM_{2.5}$), and a daily 8-hr maximum of ozone (O_3).

Ambient air quality data have been collected routinely at over 20 locations in the San Joaquin Valley since the 1970s, and these data were acquired from U.S. Environmental Protection Agency's Air Quality System database (www.epa.gov/ttn/airs/airsaqs). The station-specific daily air quality data were spatially interpolated using inverse distance-squared weighting. Data from up to four air quality measurement stations were included in each interpolation. Owing to the regional nature of O_3, NO_2, PM_{10}, and $PM_{2.5}$ concentrations, a maximum interpolation radius of 50 km was used. NO and CO were interpolated using a smaller maximum interpolation radius of 25 km, because they are directly emitted pollutants with larger spatial gradients. When a residence was located within 5 km of one or more monitoring stations, the interpolation was based solely on the nearby values.

Gaseous pollutants were measured using Federal Reference Method continuous monitors. Particulate matter data were primarily limited to those collected with Federal Reference Method samplers and Federal Equivalent Method monitors. The national air monitoring networks began measuring $PM_{2.5}$ in 1999, therefore, births with dates of conception before 1999 were not part of the analyses of $PM_{2.5}$.

The traffic metric is an indicator of traffic density calculated from distance-decayed annual average daily traffic volumes (Kan et al., 2008) surrounding the geo-coded maternal residences. Roadway link-based traffic volumes were derived from Tele-Atlas/Geographic Data Technology traffic count data in 2005 using methodologies similar to those used in other health effects studies (Gauderman et al., 2005; Kan et al., 2008). The Geographic Data Technology traffic count data were scaled to represent year 2003 traffic levels, based on county average vehicle-miles-traveled growth rates (California Department of Transportation, 2004). Density plots were generated within a geographic information system using a linear decay function that approximates the fall-off of ambient concentrations with increasing distance away from roadways (i.e., decays to background within a given distance). Traffic density represents distance-decayed annual average daily traffic volume in both directions from all roads within the circular buffer. Traffic density is computed as if the wind directions were uniformly distributed around the compass and is symmetric on both sides of each roadway. The values are computed using the density function using a kernel with a 300-m search radius and 5-m grid resolution. We considered a radius of 150 m, though in early analyses, the estimates were not considerably different.

Statistical Analysis

Analyses were conducted to examine the association between the pollutants and the traffic metric. Each pollutant and traffic density was examined by quartile as determined by the distribution in the controls. Quartiles were chosen so that the results could be more easily compared with previous studies and the controls were the best representation of the general population. Distributions of several potential covariates were examined in relation to the exposures and the outcomes: maternal race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, or other); maternal education (less than high school, high school, more than high school); age (<25, 25–35, >35 years); parity (0, 1, >1); early pregnancy multi-vitamin use (1 month before and/or first 2 months of pregnancy); active

and/or passive smoking during pregnancy; year of estimated delivery category (1997–2000, 2001–2003, 2004–2006); and infant sex.

Multivariable logistic regression analyses were conducted to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CI) reflecting the association between ambient air pollutants and traffic density and specific birth defects. Multivariable analyses were performed adjusting for maternal race/ethnicity, education and early prenatal vitamin use. These covariates were selected a priori and based on causal assumptions derived from subject matter knowledge (Hernan et al., 2002). The remaining covariates (age, parity, active and/or passive smoking, year of birth, infant sex) were examined as potential confounders in bivariate analyses (results not shown).

Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, 2011–2012). The study protocol was reviewed and approved by the institutional review boards of Stanford University and the California Department of Public Health.

RESULTS

All 874 cases and 849 of 853 controls were assigned at least one exposure metric for the first 2 months of pregnancy. Completeness for exposure assignments was 75% for CO, 85% for NO, 98% for NO_2, 98% for PM_{10}, 99% for ozone and 91% for traffic density. Among those born after January 1st 1999, 98% of the participants were assigned an estimate for $PM_{2.5}$ exposure.

A majority of study subjects were Hispanic and had at least a high school education (Table 1). A quarter of the population was exposed to active or passive smoke. Case mothers were less likely than control mothers to take multi-vitamins in early pregnancy.

Correlations of CO with NO ($r = 0.81$), NO_2 ($r = 0.73$) and $PM_{2.5}$ ($r = 0.84$) were high, which reflects the common source of motor vehicles. Ozone was negatively correlated with the traffic-related pollutants and traffic density was not strongly correlated with pollutants (data not shown).

Table 2 displays the results from the multivariable logistic regression models of each exposure and each birth defect phenotype. Only a few odds ratios had confidence intervals that did not include 1.0. The odds of esophageal atresia were increased for the highest versus lowest quartile of traffic density (aOR = 2.8; 95% CI, 1.1– 7.4) and PM_{10} exposure (aOR = 4.9; 95% CI, 1.4–17.2).

PM_{10} was associated with a decreased risk of hydrocephaly (aOR = 0.3; 95% CI, 0.1–0.9) and CO with decreased risk of anotia/microtia (aOR = 0.4; 95% CI, 0.2–0.8) and transverse limb deficiency (aOR = 0.4; 95% CI, 0.2–0.9), again reflecting highest versus lowest quartile comparisons.

DISCUSSION

In general, our findings did not indicate associations between traffic-related air pollutants and a spectrum of birth defect phenotypes, although there were a few exceptions. Increased odds of esophageal atresia were associated with higher exposure during the first 2 months of pregnancy to PM_{10} and high levels of traffic. Exposures to traffic-related air pollution were inconsistent and some were associated with decreased risks of some defects (e.g., hydrocephaly, anotia/microtia and transverse limb deficiencies), though these results were based on a very small number of cases. There was no correction for multiple testing; therefore, these associations may have arisen from chance alone.

The current study adds to a quite limited body of research on traffic-related air pollution and birth defects. Previous studies have not found consistent results examining air pollution and birth defects (Ritz et al., 2002; Gilboa et al., 2005; Kim et al., 2007; Hwang et al., 2008; Hansen et al., 2009; Rankin et al., 2009; Strickland et al., 2009; Dolk et al., 2010; Ritz, 2010; Dadvand et al., 2010, 2011; Marshall and Lock, 2010; Lupo et al., 2011; Padula et al., 2013a,2013b).

Of the previous studies examining air pollution and the birth defect phenotypes in this analysis, one study in England found suggestive but not statistically significant associations between SO_2, NO_2, and PM_{10}, and limb deficiencies, diaphragmatic hernia and hydrocephaly (Dolk et al., 2010). The observed levels of NO_2 in England were higher than those in the San Joaquin Valley of California, but the levels of PM_{10} were lower. The other studies focused generally on birth defects not included in this analysis (e.g., oral clefts and cardiac anomalies), considered all birth defects as a single outcome, or examined pollutants not included in this analysis.

There are potential limitations to this study. There is measurement error in the exposure assignment based on distance-weighted averages of the nearest monitors. Furthermore, it is unknown how much time the mother spent at her home during the first 2 months of pregnancy. For example, this could lead to potential exposure misclassification if a mother worked at a location of different exposure levels. The ambient air pollution levels also do not account for indoor sources of the studied air pollutants that may have been present. This misclassification of exposure would bias results in an unknown direction. Traffic density within a 300-m radius had spatial, but not temporal variation within the study. The traffic counts were scaled to the middle of the time period of the study.

It is unknown whether women who did versus did not participate in the study were systematically different with respect to air pollution exposure. In addition, some women had to be excluded from various aspects of the analysis because of missing data on exposure levels. Whether these considerations incurred some bias in our results is unknown. Lastly, many of the comparisons were based on relatively small sample sizes and therefore resulted in rather imprecise estimates of effect.

Strengths of the present study include the rigorous, population-based design and careful case ascertainment. The study also allowed for detailed information to be gathered as potential covariates specifically during the critical period of the first 2 months of pregnancy including

maternal residence, multi-vitamin use, and smoking. These study characteristics limited potential selection bias and confounding. This study covered a wide geographic area where some of the highest levels of air pollution exposure exist in the United States. Our study benefited from detailed air pollution metrics with precise spatial and temporal considerations and traffic density metrics based on traffic counts.

Our results contribute to a modest body of epidemio-logic evidence regarding associations between air pollution exposure and birth defects. Many of the birth defect phenotypic groups investigated have not been previously investigated for these ambient exposures.

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Table 1

Demographic Characteristics as Percent of Subjects between 1997 and 2006 in Eight Counties in the San Joaquin Valley of California (*N* = 1723)

	Percent of cases[a] (n=874)	Percent of controls[a] (n=849)	*p* Value of chi-square test
Maternal education (years)			0.20
<12	36	32	
12	25	27	
>12	38	40	
Missing	<1	<1	
Maternal race/ethnicity			0.36
White	29	31	
Foreign-born Hispanic	33	29	
U.S.- born Hispanic	26	26	
Other	12	14	
Missing	<1	<1	
Multi-vitamin use[b]			0.08
Yes	61	65	
No	37	33	
Missing	2	2	
Smoking[c]			0.41
None	75	75	
Active only	7	8	
Passive only	12	10	
Active and passive	6	6	
Missing	1	<1	
Maternal age (years)			0.32
<25	42	46	
25–35	47	44	
>35	11	10	
Infant sex			0.01
Male	58	52	
Female	42	48	
Missing	<1	0	
Plurality			<0.01
Singletons	95	99	
Multiples	5	1	
Parity			0.51
0	40	38	
1	29	31	
>1	31	32	
Year of expected delivery date			0.12

	Percent of cases[a] (n=874)	Percent of controls[a] (n=849)	*p* Value of chi-square test
1997–2000	33	37	
2001–2003	32	33	
2004–2006	35	31	

[a] Percentages may not equal 100 owing to rounding.

[b] Any folate-containing multi-vitamin use during 1 month before through 2 months after conception.

[c] Any smoking during 1 month before through 2 months after conception.

Table 2

Adjusted[a] Odds Ratios (aOR) and 95% Confidence Intervals (CI) of Birth Defects and Exposure to Pollutants[b] and Traffic Density[c] for Subjects Born between 1997 and 2006 in Eight Counties in the San Joaquin Valley of California

	Exposure levels[b]	Amniotic band syndrome and limb body wall complex		Hydrocephaly		Anotia/microtia		Esophageal atresia	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	11	Reference	15	Reference	27	Reference	7	Reference
	0.40–0.52	7	0.6 (0.2,1.7)	4	**0.2 (0.1,0.8)**	24	0.9 (0.5,1.6)	10	1.4 (0.5,3.8)
	0.53–0.71	8	0.8 (0.3,2.0)	9	0.6 (0.2,1.4)	20	0.7 (0.4,1.3)	5	0.7 (0.2,2.3)
	0.72–1.37	7	0.6 (0.2,1.6)	8	0.5 (0.2,1.2)	10	**0.4 (0.2,0.8)**	9	1.3 (0.5,3.6)
NO (ppb)	0.69–4.14	15	Reference	12	Reference	20	Reference	10	Reference
	4.15–8.15	6	0.4 (0.2,1.1)	9	0.7 (0.3,1.8)	30	1.5 (0.8,2.7)	8	0.8 (0.3,2.0)
	8.16–20.19	12	0.8 (0.4,1.9)	9	0.7 (0.3,1.8)	27	1.4 (0.7,2.6)	8	0.7 (0.3,1.9)
	20.20–67.34	6	0.4 (0.2,1.1)	10	0.8 (0.3,1.9)	15	0.8 (0.4,1.6)	10	1.0 (0.4,2.4)
NO_2 (ppb)	2.40–13.36	14	Reference	11	Reference	21	Reference	10	Reference
	13.37–16.81	10	0.8 (0.3,1.8)	13	1.2 (0.5,2.7)	41	**1.9 (1.1,3.3)**	14	1.4 (0.6,3.2)
	16.82–20.53	9	0.7 (0.3,1.7)	8	0.8 (0.3,1.9)	26	1.2 (0.7,2.3)	8	0.8 (0.3,2.0)
	20.54–38.94	12	0.9 (0.4,2.0)	12	1.1 (0.5,2.5)	16	0.8 (0.4,1.6)	12	1.2 (0.5,2.8)
PM_{10} (μg/m^3)	7.90–25.24	13	Reference	18	Reference	22	Reference	3	Reference
	25.25–33.43	10	0.7 (0.3,1.8)	10	0.5 (0.2,1.2)	36	1.6 (0.9,2.9)	13	**4.1 (1.2,14.8)**
	33.44–44.08	5	0.4 (0.1,1.2)	10	0.6 (0.3,1.3)	24	1.1 (0.6,2.1)	12	**3.9 (1.1,14.0)**
	44.09–95.32	16	1.3 (0.6,2.7)	6	**0.3 (0.1,0.9)**	21	1.0 (0.5,1.8)	15	**4.9 (1.4,17.2)**
$PM_{2.5}$ (μg/m^3)	3.57–10.93	10	Reference	15	Reference	23	Reference	12	Reference
	10.94–14.82	9	0.9 (0.4,2.4)	3	**0.2 (0.1,0.7)**	17	0.7 (0.4,1.4)	6	0.5 (0.2,1.4)
	14.83–26.12	7	0.7 (0.3,2.0)	9	0.6 (0.3,1.5)	29	1.2 (0.6,2.1)	11	0.9 (0.4,2.1)
	26.13–66.29	4	0.4 (0.1,1.4)	7	0.5 (0.2,1.2)	16	0.6 (0.3,1.3)	8	0.7 (0.3,1.7)
O_3 8–hour maximum (ppb)	10.49–29.05	7	Reference	11	Reference	24	Reference	12	Reference
	29.06–46.94	10	1.4 (0.5,3.8)	13	1.2 (0.5,2.7)	28	1.1 (0.6,2.0)	9	0.8 (0.3,1.9)
	46.95–62.64	15	2.1 (0.8,5.3)	15	1.3 (0.6,3.0)	27	1.2 (0.7,2.1)	10	0.8 (0.4,2.0)
	62.65–91.92	13	1.8 (0.7,4.7)	5	0.5 (0.2,1.3)	25	1.0 (0.6,1.9)	13	1.1 (0.5,2.5)
Traffic density[c]	0	10	Reference	8	Reference	31	Reference	7	Reference
	1–5031	11	1.5 (0.6,3.6)	10	1.9 (0.7,4.9)	17	0.8 (0.4,1.5)	11	2.6 (1.0,6.8)
	5032–16717	12	1.6 (0.7,3.8)	11	2.0 (0.8,5.2)	28	1.3 (0.7,2.3)	9	2.1 (0.7,5.7)
	16718–135991	8	1.1 (0.4,3.0)	12	2.4 (1.0,6.1)	17	0.8 (0.4,1.4)	12	**2.8 (1.1,7.4)**

	Exposure levels[b]	Intestinal atresia/stenosis		Anorectal atresia/stenosis		Hypospadias (2nd or 3rd degree)[d]		Longitudinal limb deficiency	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	12	Reference	22	Reference	15	Reference	11	Reference
	0.40–0.52	9	0.7 (0.3,1.8)	13	0.6 (0.3,1.2)	15	1.1 (0.5,2.5)	6	0.6 (0.2,1.7)

	Exposure levels[b]	Intestinal atresia/stenosis		Anorectal atresia/stenosis		Hypospadias (2nd or 3rd degree)[d]		Longitudinal limb deficiency	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
	0.53–0.71	6	0.5 (0.2,1.3)	17	0.8 (0.4,1.5)	10	0.6 (0.3,1.5)	8	0.8 (0.3,1.9)
	0.72–1.37	9	0.7 (0.3,1.8)	13	0.6 (0.3,1.2)	15	1.4 (0.6,3.0)	9	0.9 (0.4,2.2)
NO (ppb)	0.69–4.14	11	Reference	24	Reference	12	Reference	14	Reference
	4.15–8.15	9	0.8 (0.3,2.0)	17	0.7 (0.4,1.4)	15	1.2 (0.5,2.7)	8	0.6 (0.2,1.4)
	8.16–20.19	12	1.1 (0.5,2.5)	18	0.7 (0.4,1.4)	13	0.9 (0.4,2.0)	4	**0.3 (0.1,0.9)**
	20.20–67.34	10	0.9 (0.4,2.1)	16	0.7 (0.3,1.3)	19	1.7 (0.8,3.7)	13	0.9 (0.4,2.0)
NO_2 (ppb)	2.40–13.36	16	Reference	24	Reference	14	Reference	13	Reference
	13.37–16.81	11	0.7 (0.3,1.5)	32	1.3 (0.8,2.3)	20	1.3 (0.6,2.7)	10	0.8 (0.3,1.8)
	16.82–20.53	12	0.7 (0.3,1.5)	21	0.9 (0.5,1.6)	14	0.9 (0.4,2.0)	12	0.9 (0.4,2.1)
	20.54–38.94	11	0.6 (0.3,1.4)	12	0.5 (0.2,1.0)	16	1.1 (0.5,2.4)	10	0.8 (0.3,1.8)
PM_{10} (μg/m^3)	7.90–25.24	12	Reference	20	Reference	19	Reference	15	Reference
	25.25–33.43	12	1.0 (0.4,2.2)	22	1.1 (0.6,2.0)	18	0.9 (0.5,1.9)	8	0.5 (0.2,1.3)
	33.44–44.08	11	0.9 (0.4,2.0)	28	1.4 (0.8,2.6)	14	0.8 (0.4,1.7)	13	0.8 (0.4,1.8)
	44.09–95.32	15	1.1 (0.5,2.5)	19	0.9 (0.5,1.8)	15	0.8 (0.4,1.8)	9	0.6 (0.2,1.4)
$PM_{2.5}$ (μg/m^3)	3.57–10.93	9	Reference	21	Reference	14	Reference	14	Reference
	10.94–14.82	13	1.4 (0.6,3.3)	21	1.0 (0.5,1.9)	9	0.6 (0.2,1.5)	6	0.4 (0.2,1.1)
	14.83–26.12	10	1.1 (0.4,2.7)	20	0.9 (0.5,1.8)	18	1.2 (0.6,2.6)	10	0.7 (0.3,1.6)
	26.13–66.29	10	1.0 (0.4,2.7)	15	0.7 (0.3,1.4)	11	0.8 (0.3,2.0)	9	0.6 (0.3,1.5)
O_3 8–hour maximum (ppb)	10.49–29.05	15	Reference	24	Reference	17	Reference	12	Reference
	29.06–46.94	5	0.3 (0.1,1.0)	24	1.0 (0.6,1.9)	20	1.0 (0.5,2.0)	10	0.8 (0.4,2.0)
	46.95–62.64	13	0.9 (0.4,1.9)	21	0.9 (0.5,1.6)	16	0.9 (0.4,1.9)	9	0.8 (0.3,1.8)
	62.65–91.92	17	1.2 (0.6,2.4)	21	0.9 (0.5,1.6)	12	0.7 (0.3,1.5)	14	1.2 (0.5,2.7)
Traffic density[c]	0	18	Reference	28	Reference	17	Reference	12	Reference
	1–5031	11	0.9 (0.4,2.0)	18	0.9 (0.5,1.7)	6	0.6 (0.2,1.7)	5	0.6 (0.2,1.9)
	5032–16717	8	0.6 (0.3,1.5)	12	0.6 (0.3,1.2)	18	1.7 (0.8,3.5)	9	1.1 (0.5,2.8)
	16718–135991	6	0.5 (0.2,1.2)	19	1.0 (0.5,1.9)	18	2.0 (1.0,4.3)	14	1.8 (0.8,4.1)

	Exposure levels[b]	Transverse limb deficiency		Craniosynostosis		Diaphragmatic hernia	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	19	Reference	26	Reference	9	Reference
	0.40–0.52	9	0.5 (0.2,1.1)	8	**0.3 (0.1,0.7)**	14	1.6 (0.7,4.0)
	0.53–0.71	11	0.5 (0.2,1.2)	11	**0.4 (0.2,0.9)**	10	1.1 (0.4,2.8)
	0.72–1.37	7	**0.4 (0.2,0.9)**	21	0.8 (0.4,1.5)	14	1.6 (0.6,3.7)
NO (ppb)	0.69–4.14	18	Reference	16	Reference	12	Reference
	4.15–8.15	15	0.8 (0.4,1.7)	20	1.2 (0.6,2.5)	12	1.0 (0.4,2.4)
	8.16–20.19	12	0.7 (0.3,1.4)	15	0.9 (0.4,1.9)	14	1.1 (0.5,2.5)
	20.20–67.34	8	0.4 (0.2,1.1)	19	1.2 (0.6,2.3)	16	1.3 (0.6,2.9)
NO_2 (ppb)	2.40–13.36	14	Reference	23	Reference	12	Reference
	13.37–16.81	20	1.4 (0.7,2.9)	17	0.7 (0.4,1.4)	22	1.9 (0.9,3.9)
	16.82–20.53	16	1.2 (0.6,2.5)	23	1.0 (0.5,1.8)	17	1.5 (0.7,3.3)

	Exposure levels[b]	Transverse limb deficiency		Craniosynostosis		Diaphragmatic hernia	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
PM_{10} (μg/m^3)	20.54–38.94	12	0.9 (0.4,2.0)	19	0.8 (0.4,1.5)	13	1.1 (0.5,2.5)
	7.90–25.24	16	Reference	16	Reference	13	Reference
	25.25–33.43	16	1.0 (0.5,2.1)	23	1.4 (0.7,2.7)	20	1.6 (0.8,3.3)
	33.44–44.08	17	1.1 (0.5,2.2)	22	1.3 (0.7,2.6)	17	1.4 (0.6,2.9)
	44.09–95.32	12	0.7 (0.3,1.6)	22	1.3 (0.7,2.6)	14	1.1 (0.5,2.5)
$PM_{2.5}$ (μg/m^3)	3.57–10.93	16	Reference	18	Reference	10	Reference
	10.94–14.82	11	0.7 (0.3,1.6)	11	0.6 (0.3,1.3)	16	1.7 (0.8,4.0)
	14.83–26.12	13	0.8 (0.4,1.7)	10	0.5 (0.2,1.1)	14	1.4 (0.6,3.4)
	26.13–66.29	8	0.5 (0.2,1.2)	24	1.2 (0.6,2.4)	12	1.2 (0.5,2.9)
O_3 8–hour maximum (ppb)	10.49–29.05	15	Reference	24	Reference	16	Reference
	29.06–46.94	12	0.8 (0.4,1.7)	21	0.9 (0.5,1.7)	20	1.2 (0.6,2.4)
	46.95–62.64	18	1.2 (0.6,2.5)	16	0.7 (0.3,1.3)	13	0.8 (0.4,1.7)
	62.65–91.92	17	1.1 (0.5,2.3)	22	1.0 (0.5,1.8)	15	0.9 (0.5,2.0)
Traffic density[c]	0	13	Reference	25	Reference	22	Reference
	1–5031	19	2.3 (1.1,4.8)	18	1.2 (0.6,2.2)	20	1.3 (0.7,2.5)
	5032–16717	12	1.4 (0.6,3.2)	23	1.5 (0.8,2.7)	10	0.6 (0.3,1.4)
	16718–135991	10	1.1 (0.5,2.7)	13	0.9 (0.4,1.9)	6	0.4 (0.2,1.1)

The number of controls were as follows: CO (N=624), NO (N=697), NO_2 (N=814), PM_{10} (N=804), $PM_{2.5}$ (N=646), O_3 (N=815), Traffic (N=762).

NC = not calculated.

[a] Analyses are adjusted for maternal race/ethnicity, education, and vitamin use (for the month prior to and/or the first 2 months of pregnancy).

[b] Pollutant levels are reflect quartiles of exposure among controls. They are based on 24–hr average measurements (except ozone, which is a daytime 8–hr maximum) and then averaged over 1st and 2nd months of pregnancy.

[c] Dimensionless indicator based on traffic volumes within a 300–m radius and analyzed in tertiles among non–zero values.

[d] Controls for hypospadias were only male (n=443).