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Relation between Ambient Air Quality and Selected Birth Defects, Seven County Study, Texas, 1997–2000

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A population-based case-control study investigated the association between maternal exposure to air pollutants, carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter <10 μm in aerodynamic diameter during weeks 3–8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties. Controls were frequency matched to cases on year of birth, vital status, and maternal county of residence at delivery. Stationary monitoring data were used to estimate air pollution exposure. Logistic regression models adjusted for covariates available in the vital record. When the highest quartile of exposure was compared with the lowest, the authors observed positive associations between carbon monoxide and tetralogy of Fallot (odds ratio = 2.04, 95% confidence interval: 1.26, 3.29), particulate matter <10 μm in aerodynamic diameter and isolated atrial septal defects (odds ratio = 2.27, 95% confidence interval: 1.43, 3.60), and sulfur dioxide and isolated ventricular septal defects (odds ratio = 2.16, 95% confidence interval: 1.51, 3.09). There were inverse associations between carbon monoxide and isolated atrial septal defects and between ozone and isolated ventricular septal defects. Evidence that air pollution exposure influences the risk of oral clefts was limited. Suggestive results support a previously reported finding of an association between ozone exposure and pulmonary artery and valve defects.

abnormalities; air pollution; cleft lip; cleft palate; environment and public health; heart defects, congenital

Abbreviations: CI, confidence interval; OR, odds ratio; PM_{10}, particulate matter <10 μm in aerodynamic diameter.

Adverse health effects of particulate matter and gaseous air pollutants have been demonstrated in studies of laboratory animals, controlled human exposures, and population-based epidemiology (1). The epidemiologic literature shows consistent associations with respiratory and cardiovascular disease morbidity and mortality and surrogate endpoints including hospitalizations and emergency room visits (1–6). A number of epidemiologic investigations have shown adverse effects of ambient air pollution on reproductive outcomes including spontaneous abortion, fetal growth, preterm delivery, and infant mortality (7–16), with three recent reviews of this literature (17–19).

A small body of animal toxicology literature suggests that air pollutant exposure can yield adverse reproductive effects (20–27) and potentially heritable gene mutations (28–30). Other investigators have observed mutations in fetal DNA as a result of exposure to air toxics during pregnancy (31–34). This suggestive toxicology and the growing epidemiologic evidence for the reproductive toxicity (restricted fetal growth, shortened gestation) of air pollution raise the

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question of whether air pollution is also an environmental teratogen. One ecologic study found that living in areas with more versus less industrial pollution was associated with higher rates of both spontaneous abortion and congenital anomalies (35). Similarly, a Ukrainian study that compared mutation rates for 18 different congenital anomalies in three towns representing low, middle, and high pollution levels found higher mutation rates in the more polluted communities (36). A recent population-based case-control study in southern California that looked at risks of cardiac birth defects and oral clefts associated with exposure to carbon monoxide, nitrogen dioxide, ozone, and particulate matter less than10 μm in aerodynamic diameter (PM_{10}) found associations between 1) carbon monoxide exposure during the second gestational month and an increased risk of isolated ventricular septal defects and 2) ozone exposure during the second gestational month and an elevated risk of isolated aortic artery and valve defects, pulmonary artery and valve defects, and conotruncal defects (37).

We attempted to corroborate the southern California results by using data from the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of State Health Services. The state maintains a population-based, active surveillance system for major malformations diagnosed before age 1 year. Texas has an extensive network of stationary air pollution monitors placed by the US Environmental Protection Agency. We investigated the association between maternal exposures to carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and PM_{10} during weeks 3–8 of pregnancy and the risk of selected cardiac birth defects and oral clefts in livebirths and fetal deaths between 1997 and 2000 in seven Texas counties.

MATERIALS AND METHODS

Study population

The Texas Birth Defects Registry provided data on birth defect diagnoses for 7,381 livebirths and fetal deaths of infants delivered at or after 20 weeks' gestation between January 1, 1997, and December 31, 2000, to mothers residing in one of seven counties with at least 10,000 births per year (Bexar, Dallas, El Paso, Harris, Hidalgo, Tarrant, Travis). Cases with the following characteristics were excluded: 1) no vital record ($n = 183$); 2) parent aged less than 18 years at delivery ($n = 421$); 3) presence of isolated patent ductus arteriosis or patent foramen ovale ($n = 987$) because of the defects' strong association with preterm delivery; 4) missing gestational age ($n = 189$); 5) indication of maternal diabetes on the vital record (without distinction between preexisting and gestational diabetes) ($n = 346$) because maternal diabetes is a strong risk factor for congenital cardiac defects; 6) diagnosis of holoprosencephaly in addition to an oral cleft ($n = 21$) because oral clefts are a known consequence of the midline defect; and 7) missing or post office box addresses ($n = 99$). These exclusions resulted in data on 5,338 cases available for analysis.

We analyzed six clinical diagnostic groupings of isolated cardiac and oral cleft birth defects and two clinical diagnostic groupings of multiple cardiac birth defects. The previous study of air quality and birth defects analyzed eight groupings of isolated defects (37); because of small sample sizes, we analyzed multiple rather than isolated conotruncal and endocardial cushion defects. A case with an isolated defect had a cardiac defect or an oral cleft with no other major defects, although the case could have had minor birth defects. Defects were considered minor according to National Birth Defects Prevention Study guidelines (38). A case with multiple defects had a major cardiac defect or oral cleft and at least one other major defect in either the same organ system or a different organ system. The isolated clinical diagnostic groupings of aortic artery and valve defects, atrial and atrial septal defects, pulmonary artery and valve defects, ventricular septal defects, cleft palate alone, and cleft lip with or without cleft palate, and multiple clinical diagnostic groupings of conotruncal defects and endocardial cushion defects, were created to be comparable with the previous study by Ritz et al. (37). Table 1 shows the birth defects included in each of the clinical diagnostic groupings, replicating those used in the California analysis. We also devised an alternative classification scheme that was reviewed by a member of our research team (D. E. F.), a pediatric cardiologist. Lastly, we analyzed nine individual birth defects, which included all isolated, multiple, or chromosomal cases of a specific birth defect, in an effort to explore the association in more heterogeneous groupings with greater statistical power. Because we did not use hierarchical birth defect assignments, data on infants and fetuses could be analyzed more than once depending on number of diagnoses.

After we applied the relevant restrictions noted above for cases to the pool of 607,500 eligible livebirths and fetal deaths in the state vital records database, a stratified random sample of 4,580 nonmalformed controls was selected. Controls were frequency matched to cases by vital status, year, and maternal county of residence at delivery, and they were selected to ensure a control to case ratio of approximately 2 to 1 for the largest case group. The same control group was used for all analyses.

Geocoding of maternal residence

We attempted to geocode maternal residence at delivery of 5,338 cases and 4,574 controls by using the ArcGIS 8.2 and 8.3 mapping program with ESRI StreetMap (Environmental Systems Research Institute Inc., Redlands, California) as the geocoding service. We geocoded 86 percent of cases ($n = 4,570$) and 80 percent of controls ($n = 3,667$). We evaluated the characteristics of the geocoded and nongeocoded populations and found no meaningful differences with respect to factors such as maternal age, race/ethnicity, education, cigarette smoking and alcohol consumption during pregnancy, and marital status (data not shown). Cases and controls who could not be geocoded were excluded from the analysis.

Exposure assignment

The Environmental Protection Agency provided raw data for hourly (for gases) or daily (for particulate matter) air pollution concentrations for the seven study counties

TABLE 1. Clinical diagnostic groupings and birth defects included,* Seven County Study of Air Quality and Birth Defects, Texas, 1997–2000

Clinical diagnostic category	Birth defects included
Conotruncal defects (multiple)	Tetralogy of Fallot
	Common truncus
	d-Transposition of the great vessels
	Other transposition of the great vessels
	Double outlet right ventricle
Endocardial cushion and mitral valve defects (multiple)	Endocardial cushion defects
	Mitral stenosis
	Hypoplastic left heart syndrome
Pulmonary artery and valve defects (isolated)	Pulmonary artery stenosis
	Pulmonary valve stenosis
	Total anomalous pulmonary venous return
	Other pulmonary artery lesions
	Pulmonary artery/valve atresia without ventricular septal defect
Aortic artery and valve defects (isolated)	Aortic valve stenosis
	Coarctation of the aorta
	Interrupted aortic arch
	Other aortic lesions
	Aortic atresia
	Other aortic valve lesions
Ventricular septal defects (isolated)	Ventricular septal defect
	Ventricular septal defect, atrioventricular canal type
Atrial and atrial septal defects (isolated)	Ostium secundum
	Atrial septal defect
	Cor triatriatum
	Single atrium
Cleft lip with or without cleft palate (isolated)	Cleft lip
	Cleft lip with or without cleft palate
Cleft palate (isolated)	Cleft palate

* Classification scheme designed for direct comparison with results from a California study by Ritz et al. (37).

between January 1, 1996, and December 31, 2000. For gases, we calculated daily monitoring site means and number of hourly measurements contributing to each daily mean. No monitoring data were eliminated nor were any values changed. PM_{10} and ozone were monitored in all study counties, carbon monoxide and nitrogen dioxide were monitored in six counties (excluding Hidalgo), and sulfur dioxide was monitored in four counties (excluding Bexar, Hidalgo, and Travis).

The distance from each air pollution monitor to each maternal residence at delivery in that county was calculated. Separately for each pollutant, we calculated the average exposure measured at each monitor in the county during weeks 3–8 of pregnancy. Beginning with the monitor closest to the residence at delivery, we required at least 70 percent of the total number of possible daily means for gases ($\geq$30/42 daily means) or at least 70 percent of the total number of possible hourly values ($\geq$706/1,008 hourly values) to be available for the mean to be assigned to a woman. If these criteria were not met, the next closest monitor in the county was considered until the last monitor measuring the given pollutant was considered. If none of the monitors in the county met the criteria, then no exposure assignment was made. For PM_{10}, the procedure differed slightly because the majority of data was collected only every 6 days; a monitor needed to have at least 50 percent of the total number of possible daily means available ($\geq$4/7 daily means) to be assigned to a woman. There were no case-control differences in the proportion of observations assigned exposure estimates: 91 percent for carbon monoxide, 90 percent for nitrogen dioxide, 99 percent for ozone, 55 percent for sulfur dioxide, and 94 percent for PM_{10}.

For each pollutant, at least 85 percent of the calculated means were based on the monitoring data from either the first or the second closest monitor to the maternal residence. The median distances were 8.6–14.2 km, with minimum distances of 100–600 m and maximum distances of 35.5–54.4 km.

Data analysis

We conducted all analyses with SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina). We explored the distribution of covariates and exposure among cases and controls. Considered as potential confounders were alcohol consumption during pregnancy, attendant of delivery (i.e., the person who delivered the baby (physician/nurse-midwife vs. other)), gravidity, marital status, maternal age, maternal education, maternal illness, maternal race/ethnicity, parity, place of delivery, plurality, prenatal care, season of conception, and tobacco use during pregnancy, modeled as shown in tables 2 and 3. These data were obtained from the birth or fetal death certificates for both cases and controls to ensure that data quality and source would be uniform. No covariate was missing for more than 4 percent of the study population. Because we know of only one previous study in this area (37) and no established confounders of these associations, we made no a priori assumptions about which covariates should remain in the multivariable models. The covariates in the final model were determined separately for each combination of an air pollutant and individual birth defect or birth defect grouping. If removal of the covariate resulted in more than a 10 percent change in the estimate of effect, then it was included in the model.

For mutually exclusive outcome groupings (six isolated defect groupings), we conducted supplemental analyses by using polytomous logistic regression models in SAS PROC LOGISTIC (39) with a seven-level outcome variable (representing the six isolated defect groupings and controls) and generalized logits. We confirmed our PROC LOGISTIC results by using the SAS PROC CATMOD procedure. We also conducted a ''step-down'' (40) testing strategy to control the type I error rate without sacrificing statistical power. First,

TABLE 2. Characteristics (%) of controls and cases in isolated and multiple* clinical diagnostic groupings, Seven County Study of Air Quality and Birth Defects, Texas, 1997–2000

Characteristic	Controls ($n = 3,667$)	Isolated cardiac defects				Multiple cardiac defects		Isolated oral clefts	
		Aortic artery and valve defects ($n = 45$)	Atrial septal defects ($n = 192$)	Pulmonary artery and valve defects ($n = 80$)	Ventricular septal defects ($n = 503$)	Conotruncal defects ($n = 300$)	Endocardial cushion and mitral valve defects ($n = 168$)	Cleft palate ($n = 114$)	Cleft lip with or without cleft palate ($n = 317$)
Season of conception									
Winter	26.4	22.2	24.0	30.0	22.9	27.0	35.1	28.1	25.2
Spring	23.5	11.1	26.0	22.5	26.6	23.3	20.8	28.1	28.7
Summer	24.0	31.1	22.9	23.8	25.7	21.0	18.5	22.8	18.9
Fall	26.0	35.6	27.1	23.8	24.9	28.7	25.6	21.1	27.1
Plurality: multiple gestation	2.3	15.6	20.3	16.3	8.2	3.0	6.0	3.5	1.9
Maternal age (years) (mean (standard deviation))	26.8 (5.7)	28.1 (6.2)	28.1 (5.3)	27.4 (6.0)	28.7 (6.7)	27.5 (5.7)	27.5 (5.8)	28.2 (6.4)	28.1 (6.3)
Maternal education									
Less than high school	32.2	31.8	25.0	11.3	37.7	28.6	30.1	28.6	34.5
Completed high school	31.6	34.1	33.7	45.0	31.5	27.6	32.5	33.0	35.2
More than high school	36.2	34.1	41.3	43.8	30.9	43.9	37.4	38.4	30.3
Maternal race/ethnicity									
Non-Hispanic White	30.8	28.9	45.3	32.5	29.1	38.9	32.9	50.0	32.2
Non-Hispanic Black	11.9	2.2	24.7	16.3	10.6	10.1	14.4	3.5	8.3
Non-Hispanic other race	4.2	2.2	4.7	1.3	1.6	4.4	1.8	4.4	5.1
Hispanic White	52.9	66.7	25.3	50.0	58.0	46.6	50.9	41.2	54.5
Hispanic Black	0.1	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0
Hispanic other race	0.1	0.0	0.0	0.0	0.6	0.0	0.0	0.9	0.0
Marital status: unmarried	30.6	31.1	29.3	26.3	31.3	28.7	27.5	32.5	30.1
Infant sex: male	49.6	62.2	45.3	47.5	41.0	62.3	57.7	48.3	64.0
Prenatal care: no prenatal care	1.8	2.2	2.6	2.5	2.2	0.3	1.8	0.9	1.9
Gravidity: primigravid	30.5	31.8	24.1	38.5	29.0	32.2	25.5	26.8	28.6
Parity: primiparous	36.1	45.5	33.2	51.3	35.2	37.7	32.7	32.1	34.6
Any maternal illness: maternal illness noted	6.3	13.3	12.0	10.0	9.5	6.7	7.1	7.0	7.6
Maternal smoking: smoking during pregnancy	4.9	2.2	7.8	3.8	3.6	4.7	4.2	7.1	5.8
Maternal alcohol consumption: alcohol consumption during pregnancy	0.9	0.0	0.0	1.3	0.0	1.0	0.0	1.8	0.3

* Chromosomal/syndromic defects are excluded from isolated and multiple clinical diagnostic groupings.

TABLE 3. Characteristics (%) of controls and cases with individual birth defects,* Seven County Study of Air Quality and Birth Defects, Texas, 1997–2000

Characteristic	Controls ($n = 3,667$)	Atrial septal defects ($n = 1,012$)	Aortic valve stenosis ($n = 117$)	Coarctation of the aorta ($n = 216$)	Endocardial cushion defects ($n = 107$)	Ostium secundum ($n = 430$)	Pulmonary artery atresia without ventricular septal defects ($n = 105$)	Pulmonary valve stenosis ($n = 517$)	Tetralogy of Fallot ($n = 144$)	Ventricular septal defects ($n = 1,946$)
Season of conception										
Winter	26.4	27.6	30.8	23.6	26.2	26.5	26.7	26.7	25.0	26.0
Spring	23.5	23.0	18.8	17.1	23.4	23.3	16.2	23.6	20.8	23.4
Summer	24.0	26.0	23.9	27.3	25.2	22.6	20.0	24.4	22.9	24.6
Fall	26.0	23.4	26.5	31.9	25.2	27.7	37.1	25.3	31.3	26.1
Plurality: multiple gestation	2.3	7.2	2.6	6.5	0.9	6.3	4.8	6.8	5.6	5.6
Maternal age (years) (mean (standard deviation))	26.8 (5.7)	28.1 (6.2)	28.1 (5.3)	27.4 (6.0)	28.7 (6.7)	27.9 (6.2)	28.2 (6.4)	28.1 (6.3)	28.4 (6.6)	27.5 (6.2)
Maternal education										
Less than high school	32.2	28.9	30.2	27.5	26.4	36.3	35.3	27.6	30.3	33.0
Completed high school	31.6	31.1	29.3	32.7	33.0	28.9	25.5	31.8	25.4	33.0
More than high school	36.2	40.0	40.5	39.8	40.6	34.8	39.2	40.6	44.4	34.0
Maternal race/ethnicity										
Non-Hispanic White	30.8	36.6	45.3	44.2	30.8	34.6	28.6	36.1	34.7	33.0
Non-Hispanic Black	11.9	16.8	6.8	8.4	15.9	14.3	14.3	12.9	11.8	11.0
Non-Hispanic other race	4.2	4.2	1.7	2.8	0.0	2.3	4.8	3.7	4.9	2.1
Hispanic White	52.9	42.3	46.2	44.7	53.3	48.4	51.4	47.1	48.6	53.4
Hispanic Black	0.1	0.1	0.0	0.0	0.0	0.5	1.0	0.2	0.0	0.1
Hispanic other race	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
Marital status: unmarried	30.6	30.6	20.5	25.1	29.0	28.2	37.1	26.8	23.6	29.2
Infant sex: male	49.6	52.5	65.8	54.2	52.3	44.9	53.3	52.2	50.0	47.0
Prenatal care: no prenatal care	1.8	2.8	3.4	1.9	1.9	1.9	1.0	2.1	2.8	1.9
Gravidity: primigravid	30.5	30.9	28.2	31.6	27.6	26.5	29.5	30.2	28.0	30.4
Parity: primiparous	36.1	37.4	32.5	36.7	35.2	32.8	35.2	34.7	34.8	36.4
Any maternal illness: maternal illness noted	6.3	9.0	4.3	5.6	10.3	9.5	5.7	7.2	9.0	8.2
Maternal smoking: smoking during pregnancy	4.9	5.3	4.3	4.6	3.9	6.5	1.0	5.9	4.2	4.5
Maternal alcohol consumption: alcohol consumption during pregnancy	0.9	1.3	0.9	0.9	0.0	0.7	1.0	1.0	2.8	0.9

* Individual birth defects may be isolated, multiple, or chromosomal.

we tested the hypothesis of no association between each pollutant and any of the six isolated birth defect groupings as a group. We then ''stepped down'' to conduct pollutant-defect-specific hypothesis tests of no association between each pollutant and each isolated birth defect grouping considering all exposure quartiles in a single test. We also tested the hypothesis of a linear trend in the quartile estimates and report these p values in tables 4 and 5.

We modeled air pollution exposure by using a continuous exposure metric and with quartiles based on the pollutant distributions among the controls, using the lowest quartile as the referent category. Both single-pollutant and multiple-pollutant analyses were conducted. Potential collinearity of covariates and copollutants was evaluated by using tolerance statistics (41). We also investigated potential effect measure modification by infant sex, plurality, maternal education, maternal race, and season of conception.

RESULTS

The study population is described in tables 2 and 3. Mothers of controls were approximately 1 year younger than mothers of cases. The control group tended to include a slightly larger proportion of Hispanic participants than most of the case groups with a few notable exceptions, such as for cases with isolated aortic valve defects (table 2). Males were more prevalent in some case groups, such as cleft lip with or without cleft palate (odds ratio (OR) = 1.81, 95 percent confidence interval (CI): 1.42, 2.29) and aortic valve stenosis (OR = 1.95, 95 percent CI: 1.33, 2.88). In contrast, there were significantly more females among cases with isolated ventricular septal defects (OR = 0.70, 95 percent CI: 0.58, 0.85). Case groups also tended to have more multiple gestations than the control group. Mothers of pulmonary artery and valve defect cases were remarkable in that they tended to have more education than mothers of controls and were more likely to be primiparous. Smoking and alcohol consumption during pregnancy did not differ markedly between the control and case groups with the exception of tetralogy of Fallot cases (table 3).

Table 4 shows the results for the eight clinical diagnostic birth defect groupings that were reported in the California study (37), and table 5 shows the results of the analyses of the nine individual defects. Odds ratio estimates and 95 percent confidence intervals from unadjusted and covariate-adjusted models were very similar; thus, only adjusted estimates are reported here. Each exposure-outcome model was adjusted for the covariates indicated in the table notes. The majority of analyses did not demonstrate strong evidence of increasing or decreasing risk with increasing exposure.

Clinical diagnostic birth defect groupings

For the clinical diagnostic birth defect groupings (table 4), when we compared the fourth quartile of exposure with the first, carbon monoxide was associated with multiple conotruncal defects (OR = 1.46, 95 percent CI: 1.03, 2.08; p trend = 0.0870), sulfur dioxide was associated with increased risk of isolated ventricular septal defects (OR = 2.16, 95 percent CI: 1.51, 3.09; p trend <0.0001), and PM_{10} was associated with increased risk of isolated atrial septal defects (OR = 2.27, 95 percent CI: 1.43, 3.60; p trend = 0.0001). PM_{10} also appeared to be associated with isolated cleft lip with or without cleft palate, although the association was statistically significant in the third quartile of exposure only. Inverse associations were noted for carbon monoxide and risk of isolated atrial septal defects, ozone and risk of isolated ventricular septal defects, sulfur dioxide and risk of isolated atrial septal defects and multiple conotruncal defects, and PM_{10} and risk of multiple endocardial cushion defects.

Individual birth defects

For individual defects (isolated, multiple, and chromosomal cases combined) (table 5), carbon monoxide exposure was associated with increased risk of tetralogy of Fallot (OR = 2.04, 95 percent CI: 1.26, 3.29; p trend = 0.0017), sulfur dioxide exposure was associated with increased risk of ventricular septal defects (OR = 1.31, 95 percent CI: 1.06, 1.61; p trend = 0.0850), and PM_{10} exposure was associated with increased risk of atrial septal defects (OR = 1.26, 95 percent CI: 1.03, 1.55; p trend = 0.0096). We also noted several inverse associations: carbon monoxide exposure and atrial septal defects, nitrogen dioxide exposure and ventricular septal defects, and sulfur dioxide exposure and atrial septal defects and ostium secundum. Results were similar, but less precise when we excluded cases with chromosomal anomalies (data not shown).

Simultaneous adjustment for copollutants decreased precision but did not result in meaningful changes in the estimates of the effect of individual pollutants (data not shown). Our analysis did not reveal any evidence of meaningful effect measure modification by infant sex, plurality, maternal education, maternal race, or season of conception (data not shown).

We also modeled these associations by using continuous air pollution variables to calculate a slope per unit change in exposure (data not shown). The results of the continuous models corroborated the quartile findings. For example, a 1-ppm increase in carbon monoxide exposure was associated with increased risk of tetralogy of Fallot (OR = 3.01, 95 percent CI: 1.67, 5.42), and a 10-$\mu g/m^3$ increase in PM_{10} exposure was associated with increased risk of isolated atrial septal defects (OR = 1.33, 95 percent CI: 1.11, 1.60).

We conducted two subgroup analyses to assess the robustness of our results to changes in outcome and exposure definitions. First, restricting the analysis to 3,544 heart defect cases (89 percent) who had a cardiac diagnosis confirmed by one of four diagnostic methods (cardiac catheterization, echocardiography, surgery, or autopsy) (37, 38, 42) resulted in no remarkable changes in any of the associations with respect to the magnitude, direction, or exposure-response trends (data not shown). The consistency of our results suggests that the group with confirmed cardiac defects did not differ from those with unconfirmed diagnoses. Our second subgroup analysis restricted the study population to those located within 10 km of the assigned monitor for a particular air pollutant. Depending on the defect and pollutant under

TABLE 4. Adjusted odds ratios and 95 percent confidence intervals for isolated and multiple* clinical diagnostic groupings, by quartiles of average concentration during weeks 3–8 of pregnancy, Seven County Study of Air Quality and Birth Defects, Texas, 1997–2000

Pollutant concentration	Isolated cardiac defects								Multiple cardiac defects				Isolated oral clefts			
	Aortic artery and valve defects		Atrial septal defects		Pulmonary artery and valve defects		Ventricular septal defects		Conotruncal defects		Endocardial cushion and mitral valve defects		Cleft lip with or without cleft palate		Cleft palate	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Carbon monoxide (ppm)																
Cases (no.)	41		180		60		441		280		154		293		106	
Controls (no.)	3,279		3,323		3,268		3,249		3,298		3,323		3,309		3,279	
<0.4	1.00‡,§,¶		1.00§,#		1.00‡,¶,#,**		1.00‡,§,¶,#,**,††		1.00‡		1.00§,¶		1.00¶,**,††		1.00‡,§,¶,#,‡‡,§§,¶¶	
0.4–<0.5	1.45	0.52, 4.06	0.79	0.53, 1.17	1.91	0.89, 4.12	0.78	0.58, 1.05	1.38	0.97, 1.97	0.97	0.59, 1.57	1.23	0.87, 1.75	0.90	0.50, 1.60
0.5–<0.7	1.69	0.62, 4.58	0.46	0.29, 0.73	2.06	0.91, 4.35	0.79	0.59, 1.06	1.17	0.81, 1.70	1.02	0.63, 1.65	1.09	0.77, 1.56	1.19	0.69, 2.03
≥0.7	1.61	0.59, 4.38	0.52	0.33, 0.82	0.79	0.31, 2.04	1.14	0.86, 1.51	1.46	1.03, 2.08	1.46	0.92, 2.33	1.26	0.88, 1.81	1.06	0.59, 1.89
p for trend	0.3243		0.0008		0.6729		0.3679		0.0870		0.1141		0.3109		0.6277	
Nitrogen dioxide (pphm†)																
Cases (no.)	41		180		62		451		275		152		285		104	
Controls (no.)	3,271		3,213		3,244		3,271		3,225		3,291		3,237		3,271	
<1.3	1.00‡,¶,#		1.00§,¶,#,‡‡,##,***,†††		1.00‡,¶		1.00§,¶		1.00‡,§,¶¶		1.00¶		1.00§,¶,**		1.00§,¶	
1.3–<1.7	0.61	0.19, 1.97	1.19	0.75, 1.88	1.19	0.57, 2.50	0.63	0.47, 0.84	1.03	0.73, 1.46	0.63	0.40, 1.00	0.86	0.61, 1.23	0.92	0.51, 1.63
1.7–<2.1	1.41	0.54, 3.70	1.88	1.22, 2.89	1.68	0.83, 3.39	0.81	0.62, 1.07	0.94	0.66, 1.34	0.55	0.34, 0.89	1.01	0.72, 1.41	1.07	0.61, 1.86
≥2.1	1.54	0.59, 4.00	0.61	0.33, 1.10	0.94	0.40, 2.17	0.86	0.64, 1.15	1.17	0.82, 1.66	0.78	0.50, 1.23	0.82	0.56, 1.19	1.30	0.72, 2.34
p for trend	0.1700		0.2649		0.9116		0.6830		0.5159		0.2365		0.4511		0.3272	
Ozone (pphm)																
Cases (no.)	44		192		74		490		289		165		305		114	
Controls (no.)	3,628		3,628		3,548		3,594		3,559		3,608		3,594		3,608	
<1.8	1.00¶		1.00¶		1.00§,¶,#,‡‡,##,***,†††		1.00¶,**		1.00‡,§,¶,††,¶¶		1.00§,¶		1.00¶,**		1.00§,¶	
1.8–<2.5	0.76	0.30, 1.95	0.83	0.50, 1.36	1.40	0.64, 3.05	0.83	0.61, 1.11	0.91	0.62, 1.33	1.10	0.66, 1.83	1.07	0.73, 1.55	1.07	0.57, 2.01
2.5–<3.1	0.47	0.14, 1.66	1.12	0.65, 1.94	1.43	0.58, 3.48	0.61	0.43, 0.85	0.88	0.56, 1.37	1.09	0.61, 1.96	1.14	0.74, 1.75	1.06	0.53, 2.13
≥3.1	1.56	0.53, 4.60	1.48	0.85, 2.57	1.74	0.70, 4.33	0.64	0.48, 0.90	1.09	0.70, 1.70	1.41	0.78, 2.52	1.09	0.70, 1.69	1.02	0.50, 2.08
p for trend	0.6409		0.1087		0.2683		0.0034		0.7636		0.2942		0.6705		0.9686	

Sulfur dioxide (ppb)

Cases (no.)	20		137		34		278		176		96		185		59	
Controls (no.)	1,980		2,007		1,980		1,991		2,021		1,984		1,991		1,971	
<1.3	1.00‡,§,¶,#,‡‡,##		1.00§		1.00‡,§,¶,##		1.00¶,**		1.00¶		1.00‡,‡‡,#		1.00**		1.00‡,§,¶,##	
1.3–<1.9	NA†		1.22	0.79, 1.88	0.63	0.23, 1.74	1.02	0.68, 1.53	0.71	0.46, 1.09	0.89	0.50, 1.61	0.79	0.52, 1.20	0.89	0.40, 1.97
1.9–<2.7	1.06	0.34, 3.29	0.76	0.47, 1.23	0.93	0.36, 2.38	1.13	0.76, 1.68	0.71	0.46, 1.09	0.89	0.49, 1.62	0.95	0.64, 1.43	1.49	0.72, 3.06
≥2.7	0.83	0.26, 2.68	0.42	0.22, 0.78	1.07	0.43, 2.69	2.16	1.51, 3.09	0.58	0.37, 0.91	1.18	0.68, 2.06	0.75	0.49, 1.15	1.22	0.56, 2.66
p for trend	0.9487		0.0017		0.7012		<.0001		0.0249		0.5851		0.3308		0.3713	

Particulate matter ($\mu g/m^3$)

Cases (no.)	38		189		76		464		276		158		290		102	
Controls (no.)	3,401		3,431		3,372		3,398		3,383		3,450		3,450		3,383	
<19.5	1.00‡,¶,#,§§		1.00§,#		1.00¶,#,**		1.00§,¶,#,**,††,‡‡,¶¶,##		1.00‡,§,¶,¶¶		1.00¶		1.00¶,††		1.00‡,§,¶,¶¶,##,***	
19.5–<23.8	0.40	0.15, 1.03	1.41	0.86, 2.31	1.14	0.62, 2.10	0.83	0.61, 1.11	1.13	0.79, 1.62	0.82	0.54, 1.25	1.29	0.90, 1.85	0.99	0.55, 1.78
23.8–<29.0	0.45	0.18, 1.13	2.13	1.34, 3.37	0.79	0.41, 1.55	1.12	0.85, 1.48	1.20	0.84, 1.72	0.66	0.42, 1.05	1.45	1.01, 2.07	1.14	0.64, 2.03
≥29.0	0.68	0.28, 1.65	2.27	1.43, 3.60	0.68	0.33, 1.40	0.98	0.73, 1.32	1.26	0.86, 1.84	0.63	0.38, 1.03	1.37	0.94, 2.00	1.11	0.60, 2.06
p for trend	0.4860		0.0001		0.1945		0.6129		0.2281		0.0468		0.0851		0.6431	

* Chromosomal/syndromic defects are excluded from isolated and multiple clinical diagnostic groupings.
† OR, odds ratio; CI, confidence interval; pphm, parts per hundred million; NA, not applicable.
‡ Final models adjusted for maternal education.
§ Final models adjusted for maternal race/ethnicity.
¶ Final models adjusted for season of conception.
# Final models adjusted for plurality.
** Final models adjusted for parity.
†† Final models adjusted for infant sex.
‡‡ Final models adjusted for maternal age.
§§ Final models adjusted for marital status.
¶¶ Final models adjusted for prenatal care.
Final models adjusted for maternal illness.
*** Final models adjusted for gravidity.
††† Final models adjusted for tobacco use.

TABLE 5. Adjusted odds ratios and 95 percent confidence intervals for individual* birth defects, by quartiles of average concentration during weeks 3–8 of pregnancy, Seven County Study of Air Quality and Birth Defects, Texas, 1997–2000

Pollutant concentration	Aortic valve stenosis		Atrial septal defects		Coarctation of the aorta		Endocardial cushion defects		Ostium secundum	
	OR†	95% CI†	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Carbon monoxide (ppm)										
Cases (no.)	103		862		188		100		402	
Controls (no.)	3,323		3,279		3,249		3,279		3,275	
<0.4	1.00§,¶,††,‡‡,¶¶		1.00‡,§		1.00‡,§,¶,#,**,††		1.00‡,§,¶,#,††,‡‡,¶¶		1.00‡,¶,#,††,‡‡,¶¶,##,***	
0.4–<0.5	1.01	0.57, 1.80	0.99	0.81, 1.22	1.44	0.93, 2.23	0.57	0.31, 1.04	1.15	0.85, 1.55
0.5–<0.7	0.80	0.43, 1.46	0.96	0.78, 1.19	1.24	0.80, 1.93	0.94	0.55, 1.60	0.94	0.69, 1.27
≥0.7	1.35	0.77, 2.38	0.79	0.64, 0.99	0.97	0.61, 1.56	0.86	0.49, 1.52	1.06	0.78, 1.44
p for trend	0.4732		0.0429		0.7561		0.9447		0.9450	
Nitrogen dioxide (pphm†)										
Cases (no.)	101		862		183		99		400	
Controls (no.)	3,271		3,237		3,195		3,244		3,244	
<1.3	1.00§,¶		1.00§,#,**,‡‡,¶¶,##		1.00‡,§,¶,#,**,††		1.00‡		1.00‡,¶	
1.3–<1.7	0.59	0.33, 1.09	1.30	1.05, 1.61	0.71	0.46, 1.09	0.55	0.32, 0.96	1.01	0.75, 1.35
1.7–<2.1	0.63	0.34, 1.15	1.34	1.08, 1.66	0.67	0.43, 1.04	0.51	0.29, 0.90	0.88	0.65, 1.18
≥2.1	1.16	0.67, 2.01	0.79	0.62, 1.00	0.96	0.62, 1.47	0.72	0.43, 1.21	0.77	0.56, 1.06
p for trend	0.5901		0.0742		0.7842		0.2109		0.0658	
Ozone (pphm)										
Cases (no.)	114		965		209		106		427	
Controls (no.)	3,608		3,529		3,574		3,578		3,608	
<1.8	1.00§,¶,¶¶		1.00‡,§,¶,#,**,‡‡,##		1.00§,¶,**		1.00‡,¶		1.00§,¶	
1.8–<2.5	0.97	0.52, 1.80	0.90	0.71, 1.14	1.20	0.78, 1.86	1.61	0.85, 3.06	1.02	0.74, 1.39
2.5–<3.1	1.13	0.56, 2.28	0.89	0.68, 1.16	0.94	0.55, 1.60	1.47	0.70, 3.10	0.76	0.53, 1.10
≥3.1	1.43	0.71, 2.89	1.06	0.81, 1.39	1.21	0.71, 2.06	1.61	0.75, 3.42	0.83	0.57, 1.20
p for trend	0.2948		0.7076		0.7047		0.2860		0.1561	
Sulfur dioxide (ppb)										
Cases (no.)	63		573		109		61		242	
Controls (no.)	2,020		2,007		2,007		2,020		2,007	
<1.3	1.00‡‡		1.00§		1.00§,¶		1.00¶,‡‡,##		1.00§,¶	
1.3–<1.9	1.33	0.67, 2.63	1.07	0.84, 1.36	0.90	0.50, 1.59	0.43	0.19, 0.96	0.77	0.53, 1.11

1.9–<2.7	0.34	0.12, 0.93	0.77	0.60, 0.99	0.97	0.55, 1.70	0.76	0.38, 1.52	0.76	0.52, 1.10
≥2.7	1.59	0.82, 3.09	0.43	0.31, 0.58	1.10	0.63, 1.91	0.86	0.43, 1.71	0.64	0.43, 0.95
p for trend	0.9870		<.0001		0.6977		0.9154		0.0336	
					Particulate matter (mg/m^3)					
Cases (no.)	109		977		198		98		391	
Controls (no.)	3,383		3,431		3,431		3,383		3,383	
<19.5	1.00‡,§,¶, ††,‡‡, §§,¶¶,##		1.00§,#		1.00§,¶		1.00‡,§,¶, #,‡‡,§§, ¶¶,##		1.00‡,§,¶, #,‡‡,§§	
19.5–<23.8	0.91	0.53, 1.57	1.10	0.89, 1.35	0.78	0.53, 1.15	0.87	0.49, 1.55	1.15	0.85, 1.55
23.8–<29.0	0.86	0.50, 1.50	1.28	1.04, 1.57	0.68	0.45, 1.02	1.12	0.64, 1.96	1.13	0.83, 1.53
≥29.0	1.12	0.63, 1.99	1.26	1.03, 1.55	0.75	0.48, 1.15	0.89	0.47, 1.65	1.06	0.77, 1.48
p for trend	0.7663		0.0096		0.1485		0.9133		0.7611	

	Pulmonary artery atresia without ventricular septal defects		Pulmonary valve stenosis		Tetralogy of Fallot		Ventricular septal defects	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
					Carbon monoxide (ppm)			
Cases (no.)	91		448		136		1,757	
Controls (no.)	3,264		3,323		3,343		3,342	
<0.4	1.00‡,¶,‡‡, †††		1.00§,¶,#,‡‡		1.00 NC†		1.00¶,‡‡	
0.4–<0.5	1.37	0.73, 2.58	1	0.76, 1.33	0.92	0.52, 1.62	1.03	0.87, 1.22
0.5–<0.7	0.83	0.41, 1.67	0.95	0.71, 1.25	1.27	0.75, 2.14	1.00	0.85, 1.19
≥0.7	1.62	0.87, 3.01	0.87	0.65, 1.18	2.04	1.26, 3.29	1.15	0.97, 1.36
p for trend	0.3475		0.3315		0.0017		0.1463	
					Nitrogen dioxide (pphm)			
Cases (no.)	91		438		134		1,729	
Controls (no.)	3,164		3,271		3,291		3,291	
<1.3	1.00‡,§,¶,#,**, ††,‡‡,§§, ¶¶,†††		1.00§		1.00¶		1.00¶	
1.3–<1.7	1.08	0.58, 1.99	0.87	0.67, 1.14	1.01	0.59, 1.73	0.80	0.68, 0.95
1.7–<2.1	0.82	0.43, 1.56	0.79	0.60, 1.04	1.06	0.63, 1.81	0.78	0.66, 0.92
≥2.1	0.96	0.51, 1.84	0.78	0.58, 1.04	1.56	0.93, 2.61	0.76	0.64, 0.91
p for trend	0.7087		0.0659		0.0927		0.0027	
					Ozone (pphm)			
Cases (no.)	103		500		142		1,935	
Controls (no.)	3,608		3,559		3,628		3,628	
<1.8	1.00§,¶,‡‡		1.00‡,§,¶		1.00¶		1.00¶	

Table continues

TABLE 5. Continued

	Pulmonary artery atresia without ventricular septal defects		Pulmonary valve stenosis		Tetralogy of Fallot		Ventricular septal defects	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
1.8–<2.5	0.78	0.43, 1.42	1.15	0.85, 1.55	0.81	0.47, 1.41	1.01	0.85, 1.20
2.5–<3.1	0.74	0.36, 1.53	1.01	0.71, 1.42	1.00	0.53, 1.88	0.84	0.69, 1.03
≥3.1	0.92	0.44, 1.91	0.99	0.70, 1.41	1.41	0.75, 2.64	0.89	0.72, 1.09
p for trend	0.8054		0.7917		0.2469		0.1018	
			Sulfur dioxide (ppb)					
Cases (no.)	52		273		85		1,007	
Controls (no.)	1,942		1,971		1,971		1,991	
<1.3	1.00‡,§,¶,**,‡‡		1.00‡,§,¶,#, ‡‡,##		1.00¶,‡‡		1.00**	
1.3–<1.9	0.61	0.25, 1.48	0.98	0.67, 1.42	0.75	0.40, 1.42	0.96	0.78, 1.19
1.9–<2.7	0.91	0.41, 2.01	1.09	0.75, 1.57	0.68	0.36, 1.29	0.77	0.61, 0.96
≥2.7	1.25	0.59, 2.66	1.19	0.82, 1.72	1.10	0.61, 1.99	1.31	1.06, 1.61
p for trend	0.3913		0.3001		0.8574		0.0850	
			Particulate matter (mg/m^3)					
Cases (no.)	96		476		132		1,786	
Controls (no.)	3,448		3,383		3,401		3,398	
<19.5	1.00¶,‡‡,§§,¶¶		1.00‡,§,¶,#,‡‡		1.00‡,¶		1.00§,#,**,‡‡	
19.5–<23.8	1.93	1.08, 3.45	1.16	0.88, 1.55	1.21	0.72, 2.01	1.06	0.90, 1.24
23.8–<29.0	2.01	1.11, 3.64	1.25	0.94, 1.66	1.40	0.84, 2.33	1.10	0.94, 1.29
≥29.0	0.86	0.41, 1.83	1.27	0.94, 1.71	1.45	0.85, 2.48	1.08	0.92, 1.27
p for trend	0.7400		0.1081		0.1493		0.2938	

* Individual defects may be isolated, multiple, or chromosomal.
† OR, odds ratio; CI, confidence interval; pphm, parts per hundred million; NC, no covariates met the criteria for confounding.
‡ Final models adjusted for maternal education.
§ Final models adjusted for maternal race/ethnicity.
¶ Final models adjusted for season of conception.
# Final models adjusted for plurality.
** Final models adjusted for parity.
†† Final models adjusted for infant sex.
‡‡ Final models adjusted for maternal age.
§§ Final models adjusted for marital status.
¶¶ Final models adjusted for prenatal care.
Final models adjusted for maternal illness.
*** Final models adjusted for gravidity.
††† Final models adjusted for tobacco use.

analysis, this restriction of the study population could result in a sample size reduction of 50 percent or more. Because sample sizes were so much smaller, the associations found in this subgroup analysis were less precise than the results using the full data set, but they were generally consistent with respect to the direction and magnitude of the associations (data not shown).

DISCUSSION

We explored the relation between five air pollutants and 17 clinical birth defect groupings and individual birth defects. The strongest evidence for increased risks was observed for 1) carbon monoxide and tetralogy of Fallot and multiple conotruncal defects, 2) sulfur dioxide and isolated ventricular septal defects and all ventricular septal defects combined, and 3) PM_{10} and isolated atrial septal defects. We also noted a number of inverse associations.

In a similar study in California, Ritz et al. (37) reported an association between carbon monoxide and isolated ventricular septal defects, which we were unable to replicate. They also reported an association between ozone exposure and increased risk of isolated pulmonary artery and valve defects (OR = 1.36 for quartile 2, OR = 1.42 for quartile 3, and OR = 1.99 for quartile 4). Our odds ratio estimates for this association were of similar magnitude and precision to the California results. Ritz et al. also reported an association between ozone and risk of isolated aortic artery and valve defects (OR = 1.19 for quartile 2, OR = 1.69 for quartile 3, and OR = 2.68 for quartile 4), which we did not see in our data, although the risk of aortic valve stenosis was elevated (OR = 0.97 for quartile 2, OR = 1.13 for quartile 3, and OR = 1.43 for quartile 4). The Ritz et al. California study also noted an association between ozone exposure and conotruncal defects (OR = 1.63 for quartile 2, OR = 1.98 for quartile 3, and OR = 2.50 for quartile 4). We had sufficient data to analyze only the grouping of multiple conotruncal defects ($n = 300$) and found no association with ozone exposure, although we did find a suggested association with carbon monoxide exposure (table 4). We expected consistency between our ozone results and those from the California study because the ozone levels were comparable. The California study looked at PM_{10} and reported no associations with any isolated defects. Our study found a noteworthy association between PM_{10} and isolated atrial septal defects and a suggested association between PM_{10} and isolated cleft lip with or without cleft palate. The California study did not investigate the effects of sulfur dioxide, providing no source of comparison for our sulfur dioxide results.

A number of factors may explain the differences between our results and those of the California study (37). The carbon monoxide levels in the seven-county region of Texas were much lower and much less variable than those reported in southern California (California's 25th percentile for carbon monoxide exposure was approximately twice as high as the 75th percentile in Texas, and the difference between quartiles 4 and 1 was 1.3 ppm in California and 0.3 ppm in our study). We used a different critical window of exposure in our analyses. Ritz et al. (37) examined gestational-month-specific exposures, while we calculated a mean exposure for the entire period of susceptibility, from gestational weeks 3 through 8.

Our study had several notable strengths. We conducted a large, population-based analysis using a high-quality birth defects registry with rich air pollution monitoring data. To our knowledge, our study was the first to analyze individual birth defects as well as clinical diagnostic birth defect groupings. We looked at a presumed etiologically relevant exposure window and adjusted for many potential confounders. Despite these efforts, however, residual confounding is possible, either by unmeasured or poorly characterized factors or by other environmental toxicants. A number of unmeasured factors during early pregnancy, such as use during pregnancy of a special prenatal vitamin or a general multivitamin (43–50), residential mobility (51–53), and time activity patterns such as commuting habits and time spent outside, could all be acting as confounders, effect-measure modifiers, or sources of exposure measurement error.

There were other potential sources of measurement error in our study. Our exposure assignment strategy considered the distance between the home and the monitor and the density of data available during the critical window to develop ambient air pollution exposure estimates. We did not use dispersion models or incorporate meteorologic factors, and we used relatively simple geographic techniques. It is unlikely that the resulting measurement error differed by case-control status; in our data, geographic distributions of cases and controls were similar. National data suggest that people spend about 87 percent of their time indoors, with about 69 percent in a residence (54, 55). Our exposure assignment method assumed that women spent the majority of their time at or near home and that exposure to ambient air pollutants would be correlated with indoor levels, an assumption supported by the research on exposures to particulate matter (56–59). We had no data about indoor air pollution or any information on household characteristics such as air conditioner use versus open windows, heating or cooking source, housing quality, environmental tobacco smoke exposure, or external sources of air pollution such as occupational or vehicle-related exposures, any of which could potentially confound our associations.

The study sought to support the findings of a previous study of air quality and birth defects (37) that looked at clinical birth defect groupings and to extend the evaluation by looking at individual birth defects. For comparison with the previous study and to assist future efforts, we reported the results of all quartile analyses. Because of the large number of analyses, we were faced with a significant multiple comparisons problem, and it is likely that some of our statistically significant findings could have resulted from chance. Given the 255 associations presented here (17 outcomes × five pollutants × three quartiles), we had nearly a 100 percent chance of at least one association being significant $(1 - (1 - \alpha)^n)$ if all 255 of the individual null hypotheses were true (60). Instead of applying an overly conservative adjustment (especially because we have correlated hypotheses in which, if quartile 2 of a pollutant exposure is associated with a birth defect, we would expect that quartiles 3 and 4 would be associated as well), we conducted a sequential ''step-down'' testing procedure that enabled us

to control the type I error rate (40) but present our estimates of association and calculated confidence intervals unadjusted for multiple comparisons.

Our study does not provide strong evidence that air pollution increases the risk of cardiac defects or oral clefts. However, because pathogenesis during cardiac development varies between the different types of congenital heart malformations, we did not expect to find that air pollution exposure increased the risk of all heart defects. Our results supported one of the California study's findings (37), yet we saw more suggestive associations with PM_{10} exposure than with any other single pollutant, which the California study did not detect. There is regional heterogeneity in the source of the particles and the potentially fetotoxic chemicals that adhere to their surfaces, which could explain why PM_{10} did not have similar effects in our studies. Our findings are provocative with respect to a proposed biologic mechanism that neural crest cells, essential in both embryonic heart and pharyngeal arch development (61–71), could be selectively affected by air pollution exposures, leading to conotruncal defects such as tetralogy of Fallot.

Our study contributes to a growing body of epidemiologic literature on the adverse reproductive effects of air pollution exposure. This literature supports the notion that the developing embryo and growing fetus constitute a subpopulation susceptible to air pollution exposure, with adverse effects including reduced fetal growth and shortened gestation. The literature has also suggested that air pollution exposure during pregnancy can cause somatic and heritable gene mutations (28–30, 32, 33). Our results do not provide definitive evidence that air pollution exposure is a risk factor for cardiac and oral cleft birth defects, nor do our suggestive findings implicate a single pollutant or a particular developmental process. We suggest that future studies in this area direct more attention to ozone, sulfur dioxide, and particulate matter and focus on individual birth defects in addition to isolated and multiple birth defect groupings. In addition, we suggest that animal models continue to explore how air pollutant exposure may affect neural crest cells.

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