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Authors

Padula, Amy M

Tager, Ira B

Carmichael, Suzan L

et al.

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Original Contribution

The Association of Ambient Air Pollution and Traffic Exposures With Selected Congenital Anomalies in the San Joaquin Valley of California

Amy M. Padula*, Ira B. Tager, Suzan L. Carmichael, S. Katharine Hammond, Frederick Lurmann, and Gary M. Shaw

* Correspondence to Dr. Amy M. Padula, Stanford University, 1265 Welch Road, Stanford, CA 94305-5415 (e-mail: ampadula@stanford.edu).

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Congenital anomalies are a leading cause of infant mortality and are important contributors to subsequent morbidity. Studies suggest associations between environmental contaminants and some anomalies, although evidence is limited. We aimed to investigate whether ambient air pollutant and traffic exposures in early gestation contribute to the risk of selected congenital anomalies in the San Joaquin Valley of California, 1997–2006. Seven exposures and 5 outcomes were included for a total of 35 investigated associations. We observed increased odds of neural tube defects when comparing the highest with the lowest quartile of exposure for several pollutants after adjusting for maternal race/ethnicity, education, and multivitamin use. The adjusted odds ratio for neural tube defects among those with the highest carbon monoxide exposure was 1.9 (95% confidence interval: 1.1, 3.2) compared with those with the lowest exposure, and there was a monotonic exposure-response across quartiles. The highest quartile of nitrogen oxide exposure was associated with neural tube defects (adjusted odds ratio = 1.8, 95% confidence interval: 1.1, 2.8). The adjusted odds ratio for the highest quartile of nitrogen dioxide exposure was 1.7 (95% confidence interval: 1.1, 2.7). Ozone was associated with decreased odds of neural tube defects. Our results extend the limited body of evidence regarding air pollution exposure and adverse birth outcomes.

air pollution; birth outcomes; congenital anomalies; traffic

Abbreviations: CI, confidence interval; OR, odds ratio; PM_{10}, particulate matter less than 10 μm; $PM_{2.5}$, particulate matter less than 2.5 μm.

Congenital anomalies are a leading cause of infant mortality and an important contributor to childhood and adult morbidity. Major structural congenital anomalies are diagnosed in 2%–4% of births (1). Although some can be attributed to chromosomal abnormalities or known teratogenic agents, the etiology of most cases remains unknown. Environmental contaminants have been suggested as risk factors for some anomaly groups including neural tube defects (2–4), orofacial clefts (2, 5), and gastroschisis (6).

Epidemiologic studies in the past decade have identified associations between air pollution and adverse birth outcomes, including low birth weight, preterm birth, and infant mortality (7–9). Studies focusing on congenital anomalies (3, 10–23) and their relationship with air pollutants have not produced clear results (24). Many studies have been limited to residential information at birth rather than during the first trimester, which is a known critical period for congenital anomalies. Only 1 previous study has incorporated data on traffic exposure (10). A recent systematic review suggested that 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 (24).

For the present analysis, we used data from the California Center of the National Birth Defects Prevention Study (25) and the Children's Health and Air Pollution Study (http://chaps-sjv.berkeley.edu/) to investigate whether ambient air

pollution and traffic metrics were associated with the risks of neural tube defects (spina bifida and anencephaly only), orofacial clefts, and gastroschisis in the San Joaquin Valley of California. The current study provides thorough case ascertainment and classification in a population-based case-control study and detailed exposure assessment in a region of the United States with known poor air quality.

MATERIALS AND 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 of the California Department of Public Health. Since 1997, the Center has collected data from women residing in 8 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 (i.e., not hospital based) (26). To identify cases with birth defects, highly trained data collection staff visit all hospitals that offer obstetric or pediatric services. Staff members visit cytogenetic laboratories and all clinical genetics prenatal and postnatal outpatient services to review and abstract cases, including those diagnosed prenatally with birth defects.

Cases in the current analysis included infants with anencephaly, spina bifida, gastroschisis, cleft lip with or without cleft palate, or cleft palate alone as 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. Each case was classified as "isolated" if there was no additional major unrelated congenital anomaly or as "nonisolated" if there was at least 1 unrelated major anomaly. We excluded gastroschisis cases whose clinical presentations suggested limb-body wall complexes or amniotic band sequences.

Eligible cases included livebirths, stillbirths, and pregnancy terminations and were selected from the center's surveillance system on the basis of strict eligibility criteria. Controls included nonmalformed liveborn infants randomly selected from birth hospitals to represent the population from which the cases arose (approximately 150 controls per study year). Maternal interviews were conducted by 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 the expected date of delivery. The expected date of delivery was based on self-report; if unknown, it was estimated from information in the medical records (<2% of participants) (25).

Interviews were conducted with mothers of 71% of eligible cases and 69% of controls. The present analysis includes 806 cases (215 neural tube defects; 293 cleft lip with or without cleft palate; 129 cleft palate only; 169 gastroschisis) and 849 controls with estimated delivery dates between October 1, 1997, and December 31, 2006. Mothers with diabetes (type 1 or type 2) prior to gestation were excluded. Mothers reported a full residential history from 3 months before conception through delivery, including start and stop dates for each residence. The Centers for Disease Control and Prevention geocoded the addresses by using Centrus Desktop (Pitney Bowes, Inc., Stamford, Connecticut), which combines reference street networks from Tele Atlas B. V. ('s-Hertogenbosch, Netherlands) and United States Postal Service data. Geocodes were available for the addresses of 95% of cases and 93% of controls.

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 months of pregnancy. If there was more than 1 address during the period, exposure assignments were calculated for the number of days at each residence. Exposure assignments were made if the geocodes were within the San Joaquin Valley and were available for at least 75% of each month. Daily 24-hour averages of nitrogen dioxide, nitrogen oxide, carbon monoxide, particulate matter <10 μm (PM_{10}), and particulate matter <2.5 μm ($PM_{2.5}$) and a daily 8-hour maximum of ozone and were then averaged over the first 2 months of pregnancy.

Ambient air quality data have been collected routinely at more than 20 locations in the San Joaquin Valley since the 1970s, and these data were acquired from the US Environmental Protection Agency's Air Quality System database (www.epa.gov/ttn/airs/airsaqs). The station-specific daily air quality data were spatially interpolated by using inverse distance-squared weighting. Data from up to 4 air quality measurement stations were included in each interpolation. Owing to the regional nature of ozone, nitrogen dioxide, PM_{10}, and $PM_{2.5}$ concentrations, we used a maximum interpolation radius of 50 km. Nitrogen oxide and carbon monoxide were interpolated by 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 1 or more monitoring stations, the interpolation was based solely on the nearby values.

Gaseous pollutants were measured by using Federal Reference Method (US Environmental Protection Agency, Office of Air Quality Planning and Standards, Research Triangle Park, North Carolina) 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 prior to 1999 were not part of the analyses of $PM_{2.5}$.

Traffic density indicators were calculated to represent traffic counts within a 300-m radius of early pregnancy residences. The primary traffic metric is an indicator of traffic density calculated from distance-decayed annual average daily traffic volumes (27) surrounding the geocoded maternal

Table 1. Demographic Characteristics of Subjects in 8 Counties in the San Joaquin Valley of California, 1997–2006 ($n = 1,651$)[a]

Characteristic	Controls, %	Neural Tube Defects[b], %	Cleft Lip With or Without Cleft Palate[c], %	Cleft Palate Only[d], %	Gastroschisis[e], %
Maternal education, years					
<12	32	35	31	36	40
12	27	34	30	28	37
>12	40	31	39	36	21
Missing	<1	0	0	0	2
Maternal race/ethnicity					
White	31	26	33	27	24
Foreign-born Hispanic	29	38	32	36	20
US-born Hispanic	26	27	24	22	35
Other	14	9	11	15	19
Missing	<1	<1	<1	0	2
Multivitamin use[f]					
Yes	65	65	66	60	58
No	33	31	33	39	40
Missing	2	4	1	1	2
Smoking[g]					
None	75	74	69	72	64
Active only	8	8	9	9	14
Passive only	10	15	13	12	15
Active and passive	6	3	8	8	7
Missing	<1	0	<1	0	0
Maternal age, years					
<20	18	14	12	10	41
20–24	29	26	31	27	40
25–29	25	33	29	28	11
30–34	18	18	18	19	8
≥35	10	9	10	16	<1

Table continues

residences. Roadway link–based traffic volumes were derived from 2005 Geographic Data Technology traffic count data (Geographic Data Technology, Inc./Tele Atlas, Lebanon, New Hampshire) by using methodologies similar to those used in other health effects studies (27, 28). The Geographic Data Technology traffic counts were scaled to represent 2003 traffic levels on the basis of average growth rates of vehicle-miles-traveled by county (California Department of Transportation, 2004). Density plots were generated within a geographic information system by 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 symmetrical on both sides of each roadway. The values are computed with the density function by using a kernel with a 300-m search radius and 5-m grid resolution.

Statistical analysis

Analyses were conducted to examine the association between the pollutants and traffic metrics. Each pollutant and traffic metric 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 relationship to the exposures and the

Table 1. Continued

Characteristic	Controls, %	Neural Tube Defects[b], %	Cleft Lip With or Without Cleft Palate[c], %	Cleft Palate Only[d], %	Gastroschisis[e], %
Infant sex					
Male	52	47	65	43	49
Female	48	48	35	57	51
Missing	0	4	<1	0	0
Plurality					
Singletons	99	96	97	98	100
Multiples	1	4	3	2	0
Parity					
0	38	28	32	34	62
1	30	34	33	25	26
≥2	32	38	35	41	12
Year of expected delivery					
1997–2000	37	36	33	34	30
2001–2003	32	35	32	32	30
2004–2006	31	29	34	34	40

[a] Among the total study subjects, there were 849 controls and 215 subjects with neural tube defects, 293 subjects with cleft lip with or without cleft palate, 129 subjects with cleft palate only, and 169 subjects with gastroschisis.
[b] One case with anencephaly and spina bifida is counted only as anencephaly case.
[c] One case with anencephaly and cleft lip with or without cleft palate is counted in both case groups.
[d] One case with cleft palate only and spina bifida is counted in both case groups; 1 case with cleft palate only and anencephaly is counted in both case groups.
[e] One case with gastroschisis and cleft lip with or without cleft palate is counted in both case groups.
[f] Any folate-containing multivitamin use during 1 month before through 2 months after conception.
[g] Any smoking during 1 month before through 2 months after conception.

outcomes: maternal race/ethnicity (non-Hispanic white, US-born Hispanic, foreign-born Hispanic, other); maternal education (less than high school, high school, more than high school); age (<25, 25–34, ≥35 years); parity (0, 1, >1); early pregnancy multivitamin use (1 month prior to 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's sex.

Table 2. Pearson Correlation Coefficients of Exposures[a] to Pollutants Among Controls in 8 Counties in the San Joaquin Valley of California, 1997–2006

	Carbon Monoxide	Nitrogen Oxide	Nitrogen Dioxide	Particulate Matter <10 μm	Particulate Matter <2.5 μm	Ozone	Traffic Density
Carbon monoxide	Referent						
Nitrogen oxide	0.81	Referent					
Nitrogen dioxide	0.73	0.74	Referent				
Particulate matter <10 μm	0.40	0.22	0.51	Referent			
Particulate matter <2.5 μm	0.84	0.75	0.62	0.54	Referent		
Ozone	−0.57	−0.71	−0.35	0.17	−0.61	Referent	
Traffic density	0.01	0.03	0.11	−0.01	−0.01	0.02	Referent
P Value	0.76	0.40	<0.05	0.86	0.88	0.61	<0.05

[a] Pollutant levels are based on 24-hour average measurements except ozone (8-hour maximum), and traffic density is a dimensionless indicator based on traffic volumes within a 300-m radius.

Table 3. Adjusted[a] Odds Ratios and 95% Confidence Intervals of Neural Tube Defects Including Anencephaly and Spina Bifida in 8 Counties in the San Joaquin Valley of California, 1997–2006

Exposure Levels[b]	No. of Controls	Neural Tube Defects			Anencephaly			Spina Bifida		
		No. of Cases	Adjusted OR	95% CI	No. of Cases	Adjusted OR	95% CI	No. of Cases	Adjusted OR	95% CI
Carbon monoxide, ppm										
0.13–0.39	157	27	1.00	Referent	10	1.00	Referent	17	1.00	Referent
0.40–0.52	154	35	1.35	0.78, 2.35	7	0.78	0.29, 2.12	28	1.68	0.88, 3.22
0.53–0.71	156	36	1.40	0.81, 2.43	16	1.75	0.76, 4.03	20	1.19	0.60, 2.38
0.72–1.37	157	50	1.87	1.11, 3.16	16	1.63	0.71, 3.76	34	2.00	1.06, 3.75
Nitrogen oxide, ppb										
0.69–4.14	172	37	1.00	Referent	10	1.00	Referent	27	1.00	Referent
4.15–8.15	172	31	0.88	0.52, 1.49	9	1.01	0.40, 2.56	22	0.84	0.46, 1.54
8.16–20.19	178	42	1.14	0.70, 1.87	12	1.23	0.51, 2.94	30	1.11	0.63, 1.95
20.20–67.34	175	65	1.79	1.13, 2.83	26	2.76	1.28, 5.94	39	1.44	0.84, 2.46
Nitrogen dioxide, ppb										
2.40–13.36	203	41	1.00	Referent	16	1.00	Referent	25	1.00	Referent
13.37–16.81	203	40	1.00	0.62, 1.62	14	0.90	0.43, 1.91	26	1.07	0.59, 1.92
16.82–20.53	203	53	1.3	0.88, 2.20	14	0.98	0.46, 2.07	39	1.66	0.96, 2.87
20.54–38.94	205	69	1.74	1.12, 2.69	27	1.74	0.90, 3.35	42	1.73	1.01, 2.97
Particulate matter <2.5 μm, μg/m^3										
3.57–10.93	160	31	1.00	Referent	12	1.00	Referent	19	1.00	Referent
10.94–14.82	159	32	1.06	0.61, 1.82	9	0.82	0.33, 2.01	23	1.21	0.63, 2.32
14.83–26.12	165	53	1.62	0.98, 2.67	19	1.60	0.74, 3.43	34	1.66	0.90, 3.05
26.13–66.29	162	45	1.44	0.86, 2.40	18	1.57	0.73, 3.40	27	1.36	0.72, 2.56
Particulate matter <10 μm, μg/m^3										
7.90–25.24	198	50	1.00	Referent	19	1.00	Referent	31	1.00	Referent
25.25–33.43	204	48	0.94	0.61, 1.47	20	1.08	0.56, 2.09	28	0.87	0.50, 1.51
33.44–44.08	202	44	0.89	0.56, 1.40	12	0.66	0.31, 1.40	32	1.03	0.60, 1.75
44.09–95.32	200	59	1.19	0.77, 1.82	19	1.06	0.54, 2.08	40	1.28	0.77, 2.15
Ozone, ppb										
10.49–29.05	205	68	1.00	Referent	27	1.00	Referent	41	1.00	Referent
29.06–46.94	205	49	0.70	0.46, 1.06	13	0.45	0.22, 0.90	36	0.87	0.53, 1.43
46.95–62.64	204	50	0.73	0.48, 1.10	20	0.72	0.39, 1.33	30	0.75	0.45, 1.25
62.65–91.92	201	39	0.58	0.37, 0.90	12	0.45	0.22, 0.92	27	0.66	0.39, 1.13

Table continues

Table 3. Continued

Exposure Levels[b]	No. of Controls	Neural Tube Defects			Anencephaly			Spina Bifida		
		No. of Cases	Adjusted OR	95% CI	No. of Cases	Adjusted OR	95% CI	No. of Cases	Adjusted OR	95% CI
Traffic density[c]										
0	258	59	1.00	Referent	24	1.00	Referent	35	1.00	Referent
1–5,031	168	44	1.15	0.74, 1.78	11	0.66	0.31, 1.41	33	1.46	0.87, 2.45
5,032–16,717	172	44	1.09	0.70, 1.70	17	0.98	0.50, 1.89	27	1.17	0.68, 2.02
16,718–135,991	164	36	0.95	0.60, 1.52	14	0.90	0.45, 1.83	22	0.98	0.55, 1.75

Abbreviations: CI, confidence interval; OR, odds ratio.
[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 based on 24-hour average measurements except ozone (8-hour maximum), which are then averaged over the first and second months of pregnancy and analyzed in quartiles (determined from controls).
[c] Dimensionless indicator based on traffic volumes within a 300-m radius and analyzed in tertiles among non-0 values.

Multivariable logistic regression analyses were conducted to estimate adjusted odds ratios and 95% confidence intervals reflecting the association of ambient air pollutants and traffic density with specific congenital anomalies. Multivariable analyses were performed by adjusting for maternal race/ethnicity, education, and early prenatal vitamin use. These covariates were selected a priori on the basis of causal assumptions derived from subject matter knowledge (29). The remaining covariates (age, parity, active and/or passive smoking, year of birth, and infant's sex) were examined as potential confounders in bivariate analyses (results not shown). In a secondary set of models, additional covariates were added to the original multivariable model if their *P* values were less than 0.1 and if the estimate changed by more than 10%.

Analyses of gastroschisis were stratified by maternal age (<20 and ≥20 years of age) owing to the unusual age distribution of cases. Stratum-specific odds ratios were compared to assess the role of cigarette smoking as a potential modifier.

We calculated propensity scores by using multinomial logistic regression. We examined the predicted probability of being in each quartile of each pollutant to determine whether it was necessary to rebalance the covariate structure. The distributions of predicted probabilities were similar across all quartiles for all exposures (Web Figure 1, available at http://aje.oxfordjournals.org/); therefore, a propensity score analysis was not necessary. Furthermore, the experimental treatment assignment assumption was not violated. That is, within strata of the covariates of our a priori model, the conditional probability of each level of exposure was bounded away from 0 and 1 (30).

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

RESULTS

Of the original 1,655 geocoded residences during the first 2 months of pregnancy and within the boundaries of San Joaquin Valley counties, all of the cases and 849 of the 853 controls were assigned at least 1 exposure metric. Completeness for exposure assignments was 74% for carbon monoxide, 84% for nitrogen oxide, 98% for nitrogen dioxide, 98% for PM_{10}, 98% for ozone, and 91% for traffic density. Among those born after January 1, 1999, 98% of the participants were assigned an estimate for $PM_{2.5}$ exposure. The numbers and percentages of cases and controls assigned each exposure metric are in Web Table 1.

The majority of study subjects were Hispanic, and almost half were less than 25 years of age at delivery and had at least a high school education (Table 1). The majority of cases with gastroschisis had a maternal age of less than 20 years. Approximately two thirds of women took a multivitamin early in pregnancy, and cases were more likely to be exposed to active and passive smoke compared with controls. Controls were all livebirths by definition, and 11% cases were not liveborn.

Correlations of carbon monoxide with nitrogen oxide ($r = 0.81$), nitrogen dioxide ($r = 0.73$), and $PM_{2.5}$ ($r = 0.84$) were high, which reflects the common source of motor vehicles (Table 2). Ozone was negatively correlated with the traffic-related pollutants, and traffic density was not correlated with pollutants.

Table 3 displays the results from the multivariable logistic regression models of each exposure and neural tube defects. Those in the highest exposure quartile had increased odds of neural tube defects compared with those in the lowest quartile for several pollutants (carbon monoxide, nitrogen oxide, and nitrogen dioxide) after adjusting for maternal race/ethnicity, education, and multivitamin use. The adjusted odds ratio for neural tube defects for this comparison of carbon monoxide exposure was 1.9 (95% confidence interval (CI): 1.1, 3.2) with a monotonic exposure-response across quartiles. The highest quartile of nitrogen oxide exposure was associated with neural tube defects (adjusted odds ratio (OR) = 1.8, 95% CI: 1.1, 2.8), especially anencephaly (adjusted OR = 2.8, 95% CI: 1.3, 5.9). The adjusted odds ratio for the highest quartile of nitrogen dioxide exposure was 1.7 (95% CI: 1.1, 1.7). Ozone was associated with decreased odds of neural tube defects (adjusted OR = 0.6, 95% CI: 0.4, 0.9). Local-scale exposure to traffic as measured by traffic density was not significantly associated with neural tube defects.

Similar associations were not observed for oral clefts (Table 4). We found associations in the unexpected direction between carbon monoxide and cleft lip with or without cleft palate for the each of the highest 3 quartiles compared with the lowest. The third quartile of traffic density was associated with cleft lip with or without cleft palate (adjusted OR = 1.8, 95% CI: 1.2, 2.5).

Exposures did not appear to be associated with gastroschisis (Table 5). Additional covariates did not change the estimates substantially (data not shown).

Observed patterns of associations did not differ in the stratum-specific results among those exposed to active and passive smoke.

DISCUSSION

We observed that higher exposure to the traffic-related ambient air pollutants carbon monoxide, nitrogen oxide, and nitrogen dioxide, and lower exposure to ozone during the first 2 months of pregnancy were associated with increased odds of neural tube defects in children born in the San Joaquin Valley of California. In contrast, higher carbon monoxide exposure was associated with decreased odds of cleft lip with or without cleft palate. Traffic density was associated with cleft lip with or without cleft palate. We found no associations between particulate matter and the selected birth defects.

We observed inconsistencies between findings for regional measurements of traffic-related pollutants and local-scale measurements of traffic. This has been observed in other epidemiologic studies that used the same exposures (31). One might expect the measured estimates to be more strongly correlated, and therefore results to be more similar; however, the observed discrepancy may reflect measurement error for the pollutant concentrations or the traffic density measures. For example, the monitors are designed to capture regional air pollution across time and space and are located away from sources. This may underestimate the individual exposures of those who live near traffic sources. Traffic density is an indicator of a mixture of pollutants from a single source based on traffic counts that are scaled to capture temporal trends. The differences may also reflect specific and unmeasured agents within the vehicle emissions that are responsible for the observed effects. Future studies could benefit from examining additional traffic-related pollutants, such as polycyclic aromatic hydrocarbons.

The current findings add to a relatively small body of data on air pollutants and congenital anomalies. Previous studies examining ambient air pollution and anomalies have not found consistent results (3, 12–20, 22, 23), though limited evidence has suggested an association between air pollution and some cardiac anomalies (10, 11, 21). Few studies have examined traffic-related air pollution in relation to neural tube defects or orofacial clefts, and none to our knowledge has studied air pollution and gastroschisis. Two recent studies found increased odds of neural tube defects in relation to benzene (3) and polycyclic aromatic hydrocarbons (4), which are also traffic-related pollutants.

Of 7 previous studies investigating orofacial clefts and ambient air pollution, 1 found an association between ozone and cleft lip with or without cleft palate (5), and 2 found increased odds of cleft lip with or without cleft palate with higher exposure to sulfur dioxide, which was not measured in our study (23, 17). Gilboa et al. (14) conducted a study in Texas and found limited evidence of an association between air pollutants and oral clefts. In animal studies, maternal exposure to ozone, nitrogen oxide, and carbon monoxide has produced embryotoxic effects as well as teratogenic effects, such as skeletal and neuromuscular anomalies (32–34).

Assessment of individual pollutants is difficult because air pollution constitutes a complex mixture. Carbon monoxide, nitrogen oxide, and $PM_{2.5}$ are correlated because they share common sources. Our study is unable to disentangle which pollutant(s) may be responsible for the observed associations. Ozone is a secondary air pollutant that is generated by the interaction of sunlight and vehicle emissions. Furthermore, ozone is negatively correlated with traffic-related air pollutants because of photochemistry, which varies with seasonal changes.

The association between maternal smoking and congenital anomalies (and other adverse birth outcomes) provides a biological rationale for the investigation of the influence of ambient air pollution on fetal development. Although exposure to ambient air pollution is not typically as high as exposure to maternal smoking, the exposure to ambient air pollution affects a larger population and is not modifiable at the individual level. Previous studies have found inverse associations between active smoking and neural tube defects (35); however, this may be due to earlier abortion of the fetus (i.e., left censoring). In the current study, only passive smoking was associated with spina bifida and cleft lip with or without cleft palate, and only active smoking was associated with gastroschisis. Active and passive smoking did not modify the results.

Table 4. Adjusted[a] Odds Ratios and 95% Confidence Intervals of Clefts, Categorized by Cleft Palate Only and Cleft Lip With or Without Cleft Palate in 8 Counties in the San Joaquin Valley of California, 1997–2006

Exposure Levels[b]	No. of Controls	Cleft Palate Only			Cleft Lip With or Without Cleft Palate		
		No. of Cases	Adjusted OR	95% CI	No. of Cases	Adjusted OR	95% CI
Carbon monoxide, ppm							
0.13–0.39	157	33	1.00	Referent	73	1.00	Referent
0.40–0.52	154	22	0.70	0.38, 1.26	43	0.60	0.38, 0.93
0.53–0.71	156	19	0.57	0.31, 1.06	42	0.58	0.37, 0.90
0.72–1.37	157	24	0.73	0.41, 1.31	45	0.60	0.38, 0.92
Nitrogen oxide, ppb							
0.69–4.14	172	30	1.00	Referent	69	1.00	Referent
4.15–8.15	172	25	0.84	0.47, 1.50	66	0.97	0.65, 1.44
8.16–20.19	178	26	0.85	0.48, 1.50	59	0.82	0.55, 1.24
20.20–67.34	175	29	0.96	0.55, 1.68	52	0.76	0.50, 1.15
Nitrogen dioxide, ppb							
2.40–13.36	203	34	1.00	Referent	84	1.00	Referent
13.37–16.81	203	30	0.87	0.51, 1.48	66	0.78	0.54, 1.14
16.82–20.53	203	31	0.90	0.53, 1.53	72	0.87	0.60, 1.26
20.54–38.94	205	31	0.90	0.53, 1.53	59	0.69	0.47, 1.02
Particulate matter <2.5 μm, μg/m^3							
3.57–10.93	160	32	1.00	Referent	63	1.00	Referent
10.94–14.82	159	24	0.75	0.42, 1.35	61	0.99	0.65, 1.51
14.83–26.12	165	25	0.76	0.43, 1.34	43	0.66	0.42, 1.04
26.13–66.29	162	24	0.74	0.41, 1.32	71	1.12	0.75, 1.69
Particulate matter <10 μm, μg/m^3							
7.90–25.24	198	33	1.00	Referent	70	1.00	Referent
25.25–33.43	204	31	0.92	0.54, 1.57	77	1.09	0.74, 1.59
33.44–44.08	202	32	0.95	0.56, 1.61	62	0.87	0.59, 1.30
44.09–95.32	200	30	0.90	0.53, 1.54	75	1.09	0.74, 1.59
Ozone, ppb							
10.49–29.05	205	28	1.00	Referent	63	1.00	Referent
29.06–46.94	205	32	1.14	0.66, 1.97	79	1.23	0.84, 1.81
46.95–62.64	204	36	1.30	0.76, 2.22	68	1.07	0.72, 1.59
62.65–91.92	201	31	1.13	0.65, 1.95	73	1.20	0.81, 1.77
Traffic density[c]							
0	258	42	1.00	Referent	74	1.00	Referent
1–5,031	168	22	0.82	0.47, 1.43	52	1.08	0.72, 1.63
5,032–16,717	172	23	0.81	0.47, 1.40	85	1.76	1.21, 2.54
16,718–135,991	164	24	0.87	0.50, 1.50	59	1.29	0.86, 1.91

Abbreviations: CI, confidence interval; OR, odds ratio.

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

[b] Pollutant levels are based on 24-hour average measurements except ozone (8-hour maximum), which are then averaged over the first and second months of pregnancy and analyzed in quartiles (determined from controls).

[c] Dimensionless indicator based on traffic volumes within a 300-m radius and analyzed in tertiles among non-0 values.

Table 5. Adjusted[a] Odds Ratios and 95% Confidence Intervals of Gastroschisis (and by Maternal Age Group) in 8 Counties in the San Joaquin Valley of California, 1997–2006

Exposure Levels[b]	Gastroschisis				Gastroschisis With Maternal Age <20 Years				Gastroschisis With Maternal Age ≥20 Years			
	No. of Cases	No. of Controls	Adjusted OR	95% CI	No. of Cases	No. of Controls	Adjusted OR	95% CI	No. of Cases	No. of Controls	Adjusted OR	95% CI
Carbon monoxide, ppm												
0.13–0.39	38	157	1.00	Referent	15	25	1.00	Referent	23	132	1.00	Referent
0.40–0.52	24	154	0.67	0.38, 1.19	9	31	0.45	0.16, 1.26	15	123	0.75	0.37, 1.54
0.53–0.71	31	156	0.88	0.51, 1.52	14	21	1.06	0.40, 2.78	17	135	0.74	0.37, 1.48
0.72–1.37	23	157	0.62	0.35, 1.10	11	22	0.78	0.28, 2.16	12	135	0.51	0.24, 1.08
Nitrogen oxide, ppb												
0.69–4.14	40	172	1.00	Referent	14	40	1.00	Referent	26	132	1.00	Referent
4.15–8.15	27	172	0.70	0.41, 1.21	13	27	1.47	0.59, 3.70	14	145	0.49	0.24, 1.00
8.16–20.19	30	178	0.79	0.46, 1.34	12	22	1.61	0.62, 4.20	18	156	0.62	0.32, 1.19
20.20–67.34	34	175	0.87	0.52, 1.46	14	23	1.61	0.64, 4.06	20	152	0.65	0.34, 1.23
Nitrogen dioxide, ppb												
2.40–13.36	47	203	1.00	Referent	16	43	1.00	Referent	31	160	1.00	Referent
13.37–16.81	44	203	0.95	0.59, 1.51	19	40	1.32	0.58, 2.97	25	163	0.80	0.45, 1.43
16.82–20.53	34	203	0.76	0.47, 1.25	16	26	1.61	0.68, 3.81	18	177	0.54	0.29, 1.01
20.54–38.94	36	205	0.75	0.46, 1.22	15	32	1.22	0.52, 2.86	21	173	0.62	0.34, 1.13
Particulate matter <2.5 μm, μg/m^3												
3.57–10.93	39	160	1.00	Referent	17	30	1.00	Referent	22	130	1.00	Referent
10.94–14.82	31	159	0.82	0.48, 1.40	8	31	0.42	0.15, 1.17	23	128	1.01	0.53, 1.95
14.83–26.12	34	165	0.87	0.51, 1.47	16	24	1.28	0.52, 3.13	18	141	0.71	0.36, 1.42
26.13–66.29	31	162	0.80	0.47, 1.38	13	24	0.88	0.35, 2.23	18	138	0.73	0.37, 1.46
Particulate matter <10 μm, μg/m^3												
7.90–25.24	44	198	1.00	Referent	16	37	1.00	Referent	28	161	1.00	Referent
25.25–33.43	45	204	0.98	0.61, 1.57	20	31	1.36	0.59, 3.13	25	173	0.83	0.46, 1.49
33.44–44.08	38	202	0.91	0.56, 1.48	14	34	0.93	0.39, 2.21	24	168	0.85	0.47, 1.55
44.09–95.32	36	200	0.80	0.49, 1.32	16	36	0.99	0.42, 2.31	20	164	0.70	0.38, 1.32
Ozone, ppb												
10.49–29.05	36	205	1.00	Referent	16	28	1.00	Referent	20	177	1.00	Referent
29.06–46.94	42	205	1.24	0.75, 2.04	17	31	1.05	0.44, 2.51	25	174	1.40	0.74, 2.65
46.95–62.64	45	204	1.21	0.74, 1.98	20	33	1.10	0.47, 2.56	25	171	1.28	0.68, 2.42
62.65–91.92	39	201	1.11	0.67, 1.85	13	49	0.48	0.20, 1.17	26	152	1.68	0.89, 3.16

Table continues

Table 5. Continued

Exposure Levels[b]	Gastroschisis				Gastroschisis With Maternal Age <20 Years				Gastroschisis With Maternal Age ≥20 Years			
	No. of Cases	No. of Controls	Adjusted OR	95% CI	No. of Cases	No. of Controls	Adjusted OR	95% CI	No. of Cases	No. of Controls	Adjusted OR	95% CI
Traffic density[c]												
0	43	258	1.00	Referent	17	35	1.00	Referent	26	223	1.00	Referent
1–5,031	33	168	1.04	0.63, 1.74	16	33	1.03	0.44, 2.43	17	135	1.08	0.56, 2.08
5,032–16,717	44	172	1.32	0.82, 2.12	15	35	0.91	0.39, 2.13	29	137	1.69	0.94, 3.05
16,718–135,991	32	164	0.98	0.59, 1.64	13	26	0.96	0.39, 2.39	19	138	1.06	0.56, 2.03

Abbreviations: CI, confidence interval; OR, odds ratio.

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

[b] Pollutant levels are based on 24-hour average measurements except ozone (8-hour maximum), which are then averaged over the first and second months of pregnancy and analyzed in quartiles (determined from controls).

[c] Dimensionless indicator based on traffic volumes within a 300-m radius and analyzed in tertiles among non-0 values.

There are some 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 each mother spent at her home during the first 2 months of pregnancy. This could lead to potential exposure misclassification if, for example, a mother worked at a location that had different exposure levels. The ambient air pollution levels also do not account for indoor sources of similar air pollutants that may have been present. This misclassification of exposure would bias results in an unknown direction. Data obtained from retrospective studies are always subject to recall error. However, recall error did not affect the exposure assignment because it was based on residential history and objective measures of air pollutant concentrations and traffic density. 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 this incurred some bias in our results is unknown.

Strengths of the present study include a 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 8 weeks of pregnancy, including maternal residence, multivitamin use, and smoking. These study characteristics limited potential selection bias and confounding. This study covered a wide geographic area with levels of air pollution that are among the highest in the United States. During the study period, counties in the study area were in nonattainment for 8-hour ozone and PM_{10} and $PM_{2.5}$ according to the National Ambient Air Quality Standards set by the US Environmental Protection Agency (http://www.epa.gov/oaqps001/greenbk/index.html). Our study benefited from detailed air pollution metrics with precise spatial and temporal considerations and traffic density metrics based on traffic counts. Finally, we thoroughly examined our data distribution to ensure our models were not extrapolating beyond the limitations of our data with respect to our covariates.

Our results suggest that exposure to increased levels of carbon monoxide, nitrogen oxide, and nitrogen dioxide during the first 8 weeks of pregnancy may contribute to the occurrence of neural tube defects (spina bifida and anencephaly) in the San Joaquin Valley of California, which is a highly polluted region of the country. Our results contribute to the body of evidence regarding air pollution exposure and adverse birth outcomes.

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Author affiliations: Department of Pediatrics, School of Medicine, Stanford University, Stanford, California (Amy M. Padula, Suzan L. Carmichael, Gary M. Shaw); Department of Epidemiology, School of Public Health, University of California Berkeley, Berkeley, California (Ira B. Tager); Department of Environmental Health Sciences, School of Public Health, University of California Berkeley, Berkeley,

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