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Ambient Air Pollution and Risk of Birth Defects in Southern California

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The authors evaluated the effect of air pollution on the occurrence of birth defects ascertained by the California Birth Defects Monitoring Program in neonates and fetuses delivered in southern California in 1987–1993. By using measurements from ambient monitoring stations of carbon monoxide (CO), nitrogen dioxide, ozone, and particulate matter <10 μm in aerodynamic diameter, they calculated average monthly exposure estimates for each pregnancy. Conventional, polytomous, and hierarchical logistic regression was used to estimate odds ratios for subgroups of cardiac and orofacial defects. Odds ratios for cardiac ventricular septal defects increased in a dose-response fashion with increasing second-month CO exposure (odds ratio $(OR)_{2nd\ quartile}$ CO = 1.62, 95% confidence interval (CI): 1.05, 2.48; $OR_{3rd\ quartile}$ CO = 2.09, 95% CI: 1.19, 3.67; $OR_{4th\ quartile}$ CO = 2.95, 95% CI: 1.44, 6.05). Similarly, risks for aortic artery and valve defects, pulmonary artery and valve anomalies, and conotruncal defects increased with second-month ozone exposure. The study was inconclusive for other air pollutants. The authors' results are supported by the specificity of the timing of the effect and some evidence from animal data; however, this is the first known study to link ambient air pollution during a vulnerable window of development to human malformations. Confirmation by further studies is needed. *Am J Epidemiol* 2002;155:17–25.

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

Recently, studies conducted in different countries such as China, the Czech Republic, Brazil, Mexico, and the United States related ambient air pollution to adverse birth outcomes, specifically low birth weight, intrauterine growth retardation, preterm birth, and fetal mortality (1–9). Our previous studies indicated that exposure to high concentrations of carbon monoxide during the last trimester of pregnancy may increase the risk of being of low weight for term birth and that exposure to carbon monoxide and particulate matter <10 μm in aerodynamic diameter (PM_{10}) either shortly after conception or before birth may trigger preterm birth (10, 11). Risks of several common birth defects including neural tube defects, oral clefts, and cardiovascular defects may be influenced by exposure to environmental contaminants (12). However, few epidemiologic studies have examined whether ambient air pollutants affect such risks.

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Abbreviations: CBDMP, California Birth Defects Monitoring Program; CI, confidence interval; OR, odds ratio; PM_{10}, particulate matter <10 μm in aerodynamic diameter.

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Mechanistically, air pollutants could be involved in the etiology of birth defects via hemodynamic, anoxic events; oxidative stress; and toxicity to certain cell populations during development. Ozone and carbon monoxide are toxic in the developing rat and produce skeletal malformations in animals (13–15). Maternal exposure to low levels of nitrogen dioxide has produced deficits in neuromuscular coordination in newborn mice (16); in humans, elevated exposure to oxidized nitrogen has been associated with poor birth outcomes such as low birth weight (17). Components of particulates such as metals or organic compounds could be fetotoxic. For example, PM_{10} has been implicated as a risk factor for infant mortality and preterm birth (7, 9, 11). However, no known animal or human studies have examined the teratogenic potential of urban air particulates.

Since California has both a population-based birth defect registry and an extensive air pollution monitoring network, we investigated whether maternal exposures to air pollution were associated with elevated birth defect risks in a cohort of southern California infants and fetuses delivered between 1987 and 1993. Vehicular traffic is the major source of air pollution in the metropolitan area of southern California and is responsible for producing carbon monoxide, nitrogen dioxide, fine components of PM_{10}, and ozone.

MATERIALS AND METHODS

Subjects and outcome

Data on birth defects were collected by the California Birth Defects Monitoring Program (CBDMP) for four counties and represented births in July 1990–July 1993 for Los Angeles,

1989 for Riverside, 1988–1989 for San Bernardino, and 1987–1989 for Orange counties. CBDMP staff actively review medical and genetics center records to ascertain cases in these surveillance areas (18). For this study, eligible cases were all liveborn infants and fetal deaths diagnosed between 20 weeks of gestation and 1 year after birth with isolated, multiple, syndromic, or chromosomal cardiac or orofacial cleft defects who 1) could be matched to California birth or fetal death registry data to obtain gestational age and zip code of residency at birth and 2) lived within 10 miles (16 km) of an air monitoring station (84 percent of all cases, of whom 78 percent were born in Los Angeles County).

Originally, we grouped isolated cardiac defects into eight diagnostic and anatomic subcategories, but since we observed too few cases in two categories to allow modeling of pollutant effects (tricuspid and Epstein anomalies (17 with complete data) and hypoplastic right heart and common ventricle anomalies (13 with complete data)), this paper presents results for six groups only: 1) aortic defects; 2) defects of the atrium and atrium septum; 3) endocardial and mitral valve defects; 4) pulmonary artery and valve defects; 5) conotruncal defects including tetralogy of Fallot, transposition of great vessels, truncus arteriosus communis, double outlet right ventricle, and aorticopulmonary window; and 6) ventricular septal defects not included in the conotruncal category. All cardiac defects were confirmed by autopsy or by surgical reports, catheterization, or echocardiogram. We divided orofacial clefts into isolated cleft palate and isolated cleft lip with or without cleft palate and examined separately all malformations attributed to a syndrome, chromosomal defects, and multiple defects, that is, all children diagnosed with more than one major anomaly. In all, we created 11 malformation groups for analyses (table 1).

Infants and fetuses were eligible as controls if 1) they were born during the same period in which the CBDMP was active in each county, they were born within at least 10 miles of an air monitoring station in a zip code area for which at least one eligible case was reported, and none of the gestational age information was missing on their birth or death certificates (86 percent of all eligible controls); and 2) they had not been diagnosed with a birth defect by age 1 year. Of the 754,030 infants and fetuses eligible as controls, we randomly selected 10,649 whose covariate information was complete (9,357 after excluding those for whom information on maternal education not recorded prior to 1989 was missing) to achieve a case-control ratio of approximately 1:10 for defect-specific analyses. Additional cases and controls were excluded from multivariate analyses because first-trimester data for one of the four air pollutants examined was missing. Birth and fetal death certificates were our only sources of risk-factor information other than air pollution measurements.

Exposure assessment

We used ambient air monitoring data for carbon monoxide, nitrogen dioxide, ozone, and PM_{10} collected by the South Coast Air Quality Management District at 30 stations between 1987 and 1993 to estimate exposure during pregnancy, in general relying on the station nearest to the residential zip code reported on birth or fetal death certificates. However, while 22 stations collected carbon monoxide and nitrogen dioxide data, and 27 collected ozone data, only 11 were equipped with PM_{10} samplers. Overall, 23 stations collected data for at least three pollutants, but no more than 10 stations collected data simultaneously for all four pollutants. In general, stations measuring all gaseous pollutants were located predominantly in the western and coastal areas of the Southern California Air Basin, while PM_{10} samplers were concentrated in the eastern and inland areas. Thus, there was little overlap between stations monitoring for the three gaseous pollutants and those monitoring for PM_{10}. Since particulate and gaseous pollutant measures were less-often collected simultaneously (e.g., carbon monoxide and PM_{10} overlapped at 11 stations only), we had to rely on stations farther removed from a residence to estimate PM_{10} exposures. A member of our research team (S. F.) manually assigned to each zip code of maternal residence the most relevant monitoring station according to distance, topography, major wind direction, and air flow in the Southern California Air Basin.

By using the recorded birth or death date and gestational age at either date, we averaged air pollution measured at the assigned ambient station over each fetus's first, second, and third month of gestation and, in addition, its second and third trimester and a 3-month period prior to conception. For these calculations, 24 hourly measurements were available for the three gaseous pollutants, but, for PM_{10}, we had to use 24-hour average measurements taken every 6 days. The relevant embryologic period for cardiac defects and orofacial defects is within the first 4–12 weeks of gestation (19, 20).

Statistical methods

The effect of ambient air pollution on birth defects was estimated by logistic regression, and, because we examined several air pollutants and birth defects, a hierarchical (two-level) regression model (a modified version of the SAS-IML program written by Witte et al. (21)) was used to adjust for multiple comparisons, as recommended by Greenland (22). The first stage of this model is a polytomous logistic regression on all 11 outcome categories; the second stage is a linear model for the parameters of the main model (second-stage model: $\beta = Z\pi + \delta$; β is the first-stage coefficient for a pollutant, Z is the matrix of second-stage covariates that predict the first-stage coefficients β, π is the vector of linear effects of the second-stage covariates (Z) on β, and δ is a vector of residual effects arising from interactions among the second-stage covariates or from covariates not in Z). The function of the second stage is to constrain the distribution of β in the first stage, that is, to shrink first-stage coefficient estimates according to some prespecified assumptions. We examined the effect of two different assumptions to define the second-stage covariates. For carbon monoxide and ozone (measured in units of ppm and pphm, respectively, but with comparable exposure ranges and effect sizes), we assumed that within the same gestational period and for all

TABLE 1. Demographic characteristics (%) of eligible children and fetuses delivered alive or dead between 1987 and 1993 in four southern California counties

	Control infants and fetuses (*n* = 10,649)	Aortic defects (*n* = 324)	Pulmonary artery and valve anomalies (*n* = 246)	Conotruncal defects (*n* = 194)	Ventricular septal defects (*n* = 313)	Atrium and atrium septum defects (*n* = 487)	Endocardial and mitral valve defects (*n* = 97)	Isolated cleft palate (*n* = 246)	Isolated cleft lip with or without palate (*n* = 630)	Multiple defects with cardiac and/or cleft defects (*n* = 254)	Chromosomal defects with cardiac and/or clefts defects (*n* = 534)	Syndromic defects with cardiac and/or clefts defects (*n* = 224)
Infant's gender												
Male	51	59	54	66	53	54	57	44	63	45	50	56
Female	49	41	46	34	47	46	43	56	37	55	50	44
No prenatal care	2	1	3	3	2	2	4	2	1	1	3	3
Multiple births	2	4	7	3	6	3	3	4	2	3	2	5
No siblings	40	38	43	40	46	41	44	43	40	39	29	41
Maternal race												
White	25	35	27	29	23	24	32	31	29	25	18	25
Hispanic	56	48	51	47	57	56	55	49	56	58	66	59
Black	10	8	13	11	10	12	6	7	5	10	7	10
Asian	6	4	5	9	7	5	4	4	6	5	5	4
Other	3	4	4	4	4	4	2	9	4	2	4	3
Maternal age (years)												
<20	12	7	15	8	14	12	11	14	9	11	7	10
20–24	27	24	21	26	24	27	26	24	32	28	15	28
25–29	29	31	29	24	27	26	30	24	29	26	20	28
30–34	21	20	22	27	21	23	23	24	20	22	23	21
≥35	11	18	13	14	13	12	10	15	10	13	34	13
Maternal education* (years)												
≤ 8	22	19	21	20	25	28	31	23	24	26	36	29
9–11	23	19	23	20	19	19	21	22	22	21	17	21
12	27	26	30	28	31	29	24	17	28	30	21	24
13–15	16	20	13	17	19	14	15	21	15	15	16	13
≥16	12	17	13	15	7	10	8	16	11	9	10	14
Born before 1990	21	23	24	30	24	14	23	24	26	19	19	17
Season of conception												
Summer	22	25	22	22	23	24	28	20	22	22	19	26
Fall	30	26	30	30	28	29	22	28	27	32	32	24
Winter	27	29	24	26	27	23	27	28	29	21	23	30
Spring	21	20	24	22	22	23	24	24	22	25	25	19

* Maternal education was not recorded on California birth or fetal death certificates prior to 1989; thus, the total numbers in each outcome category are 9,357 (controls), 282 (aortic), 213 (pulmonary), 156 (conotruncal), 268 (ventricular septal defect), 452 (atrium), 86 (endocardial), 215 (cleft palate), 540 (cleft lip with or without cleft palate), 199 (multiple), 476 (chromosomal), and 234 (syndromic).

outcome categories, 1) each pollutant-specific coefficient β has a common mean for all outcome categories, 2) both pollutant coefficients have the same common mean, and 3) the common mean is (close to) zero (no effect for pollutants). We used semi-Bayesian estimation and set the prior (second-stage) variance to 0.5, which corresponds to a prior that 95 percent of the uncertanty in the odds ratios for the factor effects, the exp (β), is within an $\exp(2(1.96 \times \sqrt{0.5})) = 16$-fold span such as 0.5 to 8.

We used indicator terms for quartiles of pollutant averages based on all subjects included in the analyses by period (month) of gestation, and this paper presents results for single- and multiple-pollutant models. The most influential gestational period of exposure was identified according to the strength and pattern of the observed effects and the width of the confidence intervals.

To allow the hierarchical models to converge in a reasonable amount of time with minimal loss of power, the size of the control group was limited to 3,000 randomly selected from the larger control group (note that polytomous regression point estimates and confidence limits changed minimally when more than 1,000 randomly selected controls were included). We adjusted for risk factors that could potentially confound the relation between outcomes and neighborhood air pollution levels. These factors were maternal age (<20, 20–24, 25–29, 30–34, >34 years), maternal race/ethnicity (White, Hispanic, Black, Asian, other), maternal education (<9, 9–11, 12, 13–15, >15 years), access to prenatal care (none vs. any), infant gender, decade of infant's birth (1980s vs. 1990s), parity (none vs. one or more), birth type (single vs. multiple), time since last pregnancy (>12 months), season of conception (spring, summer, fall, winter), and other air pollutants.

RESULTS

The distribution of demographic factors and potential risk factors for malformations is presented by case and control status in table 1. As expected, chromosomal defects were associated with advanced maternal age (>34 years) and somewhat with low maternal educational level and lack of prenatal care; isolated cleft lip with or without cleft palate affected a higher proportion of males.

Estimates derived from crude and covariate-adjusted models were almost identical; thus, crude effect estimates are not shown in table 1. When exposure quartiles were used, first-month carbon monoxide exposure exhibited some effects on both isolated cleft types but lacked a dose-response pattern for cleft palate, and effects were not observed consistently in single- and multiple-pollutant models (results not shown). No other pollutant showed a consistent effect on isolated orofacial clefts.

Dose-response patterns were observed for the following outcomes and pollutants: 1) second-month carbon monoxide exposure on ventricular septal defects (odds ratio $(OR)_{2nd\ quartile}$ carbon monoxide = 1.62, 95 percent confidence interval (CI): 1.05, 2.48; $OR_{3rd\ quartile}$ carbon monoxide = 2.09, 95 percent CI: 1.19, 3.67; $OR_{4th\ quartile}$ carbon monoxide = 2.95, 95 percent CI: 1.44, 6.05) (table 2) and 2) second-month ozone exposure on aortic artery and valve defects, pulmonary artery and valve anomalies, and conotruncal defects (table 2). Furthermore, the average effect sizes and patterns of second-month ozone exposure were similar for these defects and varied only slightly from single- to multiple-pollutant models or when we adjusted for other potential confounding factors. We did not observe consistently increased risks and dose-response patterns for nitrogen dioxide and PM_{10} after controlling for the effects of carbon monoxide and ozone on these cardiac defects (results not shown).

Adjustment for multiple comparisons using polytomous (table 3) or hierarchical logistic models (results not shown) suggested that the second-month trends for ozone and carbon monoxide for the four cardiac categories displayed in table 2 remained stable no matter which of three assumptions about a common mean was used (e.g., ventricular septal defects: $OR_{2nd\text{-}month\ carbon\ monoxide\ polytomous\ model} = 1.33$; 95 percent CI: 1.00, 1.78; $OR_{2nd\text{-}month\ carbon\ monoxide\ hierarchical\ model} = 1.32$; 95 percent CI: 1.00, 1.75; aortic defects: $OR_{2nd\text{-}month\ ozone\ polytomous\ model} = 1.56$; 95 percent CI: 1.16, 2.09; $OR_{2nd\text{-}month\ ozone\ hierarchical\ model} = 1.53$; 95 percent CI: 1.15, 2.03). A negative dose-response relation for third-month carbon monoxide and ozone exposures was observed for several outcome categories, including aortic and ventricular septal defects, chromosomal defects, and orofacial clefts (table 3). Other than a possible negative effect for first-trimester exposures, carbon monoxide and ozone were not associated with chromosomal, syndromic, or multiple malformations with cardiac or cleft defects (table 3).

Thus, for ozone and carbon monoxide, 1) we found a clear dose-response pattern for aortic septum and valve and ventricular septal defects and possibly for conotruncal and pulmonary artery and valve defects; 2) effects were comparable in size; and 3) increased risks were observed for exposures during the second month of pregnancy.

We found no consistent pattern of effects for any other pregnancy period (results not shown). Stratification according to maternal age or race did not suggest effect modification by these factors, yet the numbers of cases in most substrata were too small to be informative.

DISCUSSION

Although ambient air pollution has recently been linked to several adverse pregnancy outcomes (1–11), our results substantially extend the epidemiologic data on the potential relation between increases in ambient air pollutants during vulnerable pregnancy periods and congenital malformations. Compared with the few previous studies on this topic, our investigation 1) was large, 2) was population based, 3) enabled nearly complete ascertainment of cases, 4) examined vulnerable pregnancy periods, and 5) considered potential confounders. To our knowledge, the only previous epidemiologic information on this topic comes from ecologic studies conducted in Poland, the Czech Republic, and Russia, where communities with high versus low levels of ambient air toxics were found to have increased rates of heart defects (23), new mutations and multiple malformations (24–26), and infant mortality due to congenital mal-

TABLE 2. Odds ratios (95% confidence intervals)* for aortic and pulmonary artery and valve anomalies, ventricular septal defects, and conotruncal defects by average concentration quartile for carbon monoxide and ozone during the first 3 months of pregnancy, southern California, 1987–1993†

	Aortic artery and valve defects		Pulmonary artery and valve anomalies		Ventricular septal defects		Conotruncal defects	
	Single-pollutant model	Multiple-pollutant model	Single-pollutant model	Multiple-pollutant model	Single-pollutant model	Multiple-pollutant model	Single-pollutant model	Multiple-pollutant model
Carbon monoxide (ppm)‡								
No. of cases	276	241	209	187	260	234	152	129
No. of controls	9,106	7,944	9,106	7,944	9,106	7,944	9,106	7,944
1st month								
<1.14	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.14–<1.60	0.87 (0.60, 1.27)	0.68 (0.43, 1.07)	1.07 (0.69, 1.66)	1.16 (0.69, 1.96)	0.88 (0.59, 1.31)	1.05 (0.66, 1.68)	0.90 (0.55, 1.47)	1.10 (0.61, 2.00)
1.60–<2.47	0.80 (0.49, 1.29)	0.65 (0.35, 1.20)	1.14 (0.65, 2.01)	1.42 (0.68, 2.98)	0.77 (0.47, 1.27)	1.12 (0.59, 2.12)	0.75 (0.39, 1.45)	1.28 (0.55, 2.95)
≥2.47	0.96 (0.53, 1.73)	0.95 (0.42, 2.14)	0.96 (0.47, 1.94)	1.55 (0.59, 4.11)	0.67 (0.36, 1.23)	1.23 (0.53, 2.82)	0.79 (0.35, 1.78)	2.31 (0.76, 7.01)
2nd month								
<1.14	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.14–<1.57	1.10 (0.73, 1.66)	1.37 (0.85, 2.20)	1.09 (0.69, 1.73)	1.13 (0.67, 1.90)	1.62 (1.05, 2.48)	1.63 (1.00, 2.66)	0.79 (0.47, 1.32)	0.90 (0.48, 1.67)
1.57–<2.39	1.25 (0.74, 2.13)	1.58 (0.81, 3.07)	0.92 (0.50, 1.70)	0.97 (0.46, 2.05)	2.09 (1.19, 3.67)	1.97 (1.00, 3.91)	0.73 (0.36, 1.47)	0.69 (0.27, 1.73)
≥2.39	0.93 (0.47, 1.85)	1.03 (0.42, 2.53)	1.00 (0.46, 2.17)	1.08 (0.40, 2.92)	2.95 (1.44, 6.05)	2.84 (1.15, 6.99)	0.95 (0.38, 2.38)	0.86 (0.25, 2.87)
3rd month								
<1.12	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.12–<1.51	0.75 (0.50, 1.11)	0.73 (0.46, 1.16)	1.06 (0.68, 1.65)	1.14 (0.68, 1.91)	0.80 (0.54, 1.19)	0.77 (0.49, 1.22)	1.14 (0.70, 1.85)	1.31 (0.71, 2.42)
1.51–<2.27	0.90 (0.56, 1.44)	0.76 (0.40, 1.42)	1.18 (0.69, 2.02)	1.12 (0.56, 2.25)	0.56 (0.34, 0.93)	0.54 (0.29, 1.02)	0.62 (0.31, 1.22)	0.83 (0.34, 2.05)
≥2.27	1.27 (0.71, 2.30)	1.00 (0.45, 2.23)	1.03 (0.52, 2.05)	0.73 (0.29, 1.87)	0.55 (0.30, 1.01)	0.70 (0.31, 1.58)	0.91 (0.41, 2.05)	1.97 (0.62, 6.27)
Ozone (pphm)‡								
No. of cases	274	241	208	187	261	234	151	129
No. of controls	9,049	7,944	9,049	7,944	9,049	7,944	9,049	7,944
1st month								
<1.06	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.06–<1.94	0.99 (0.65, 1.49)	1.16 (0.72, 1.85)	1.16 (0.74, 1.83)	1.06 (0.63, 1.78)	1.00 (0.66, 1.52)	0.85 (0.53, 1.36)	0.97 (0.56, 1.70)	0.99 (0.53, 1.86)
1.94–<2.84	1.05 (0.61, 1.82)	1.30 (0.67, 2.51)	0.88 (0.47, 1.65)	0.81 (0.39, 1.69)	1.61 (0.95, 2.74)	1.38 (0.73, 2.59)	1.11 (0.54, 2.28)	1.40 (0.59, 3.32)
≥2.84	0.81 (0.42, 1.59)	1.02 (0.47, 2.23)	0.95 (0.44, 2.02)	0.87 (0.36, 2.12)	1.48 (0.76, 2.87)	1.29 (0.60, 2.78)	1.02 (0.43, 2.45)	1.44 (0.51, 4.10)
2nd month								
<1.07	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.07–<1.99	1.19 (0.71, 2.01)	0.98 (0.54, 1.78)	1.36 (0.76, 2.43)	1.49 (0.77, 2.90)	1.21 (0.73, 2.01)	1.23 (0.70, 2.16)	1.63 (0.83, 3.23)	1.83 (0.85, 3.95)
1.99–<2.86	1.69 (0.84, 3.42)	1.27 (0.56, 2.85)	1.42 (0.62, 3.23)	2.10 (0.83, 5.33)	0.94 (0.46, 1.91)	1.06 (0.49, 2.31)	1.98 (0.74, 5.31)	2.09 (0.70, 6.27)
≥2.86	2.68 (1.19, 6.05)	2.51 (0.99, 6.37)	1.99 (0.77, 5.13)	2.94 (1.00, 8.67)	1.13 (0.50, 2.54)	1.32 (0.54, 3.22)	2.50 (0.82, 7.66)	2.63 (0.75, 9.24)
3rd month								
<1.16	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.16–<2.06	0.67 (0.44, 1.02)	0.65 (0.40, 1.07)	0.71 (0.44, 1.15)	0.54 (0.30, 0.99)	1.14 (0.75, 1.74)	1.25 (0.75, 2.08)	1.23 (0.70, 2.18)	1.67 (0.82, 3.39)
2.06–<2.91	0.58 (0.34, 0.98)	0.63 (0.33, 1.19)	0.74 (0.40, 1.37)	0.53 (0.25, 1.13)	1.15 (0.67, 1.98)	1.43 (0.75, 2.74)	0.94 (0.45, 1.98)	1.11 (0.44, 2.80)
≥ 2.91	0.42 (0.22, 0.79)	0.42 (0.19, 0.91)	0.81 (0.39, 1.66)	0.56 (0.23, 1.37)	0.85 (0.44, 1.64)	1.03 (0.47, 2.27)	1.15 (0.49, 2.69)	1.39 (0.48, 4.04)

* Adjusted for the following covariates: born in the 1980s vs. 1990s, infant sex, maternal race (White, Hispanic, Black, Asian, Other), maternal age (<20, 20–24, 25–29, 30–34, >35 years), single vs. multiple birth, parity (none vs. one or more), no prenatal care, maternal education (≤ 8, 9–11, 12, 13–15, >15 years), and season of conception.

† Numbers of cases and controls vary owing to missing data for pollutants at some stations.

‡ Exposures for all 3 months of the first trimester are included in each model.

TABLE 3. Results (adjusted odds ratios (95% confidence intervals))* from polytomous logistic regression models† for carbon monoxide and ozone exposure measured continuously‡ for 11 malformation outcome categories,§ southern California, 1987–1993

	Aortic defects (n = 241)	Pulmonary valve defects (n = 185)	Conotruncal defects (n = 129)	Ventricular septal defects (n = 235)	Atrium and atrium septum defects (n = 385)	Endocardial and mitral valve defects (n = 67)
Carbon monoxide¶						
1st month	1.15 (0.89, 1.49)	1.14 (0.86, 1.53)	1.11 (0.78, 1.57)	0.97 (0.75, 1.26)	0.92 (0.75, 1.13)	0.71 (0.44, 1.15)
2nd month	0.86 (0.65, 1.14)	1.03 (0.74, 1.42)	0.98 (0.67, 1.45)	1.33 (1.00, 1.78)	1.01 (0.81, 1.28)	1.02 (0.60, 1.71)
3rd month	1.01 (0.77, 1.32)	0.94 (0.70, 1.28)	1.00 (0.69, 1.44)	0.80 (0.61, 1.05)	0.96 (0.77, 1.19)	0.91 (0.56, 1.49)
Ozone#						
1st month	0.98 (0.76, 1.27)	1.02 (0.76, 1.35)	1.07 (0.76, 1.50)	1.02 (0.79, 1.32)	1.01 (0.82, 1.24)	1.23 (0.78, 1.94)
2nd month	1.56 (1.16, 2.09)	1.34 (0.96, 1.87)	1.36 (0.91, 2.03)	1.13 (0.84, 1.52)	0.85 (0.67, 1.07)	0.81 (0.49, 1.36)
3rd month	0.70 (0.54, 0.90)	0.90 (0.68, 1.20)	0.98 (0.70, 1.38)	0.92 (0.71, 1.19)	1.01 (0.83, 1.23)	0.89 (0.57, 1.39)

	Multiple malformations with cardiac or cleft defect (n = 180)	Syndromes with cardiac or cleft defect (n = 200)	Chromosomal malformations with cardiac or cleft defect (n = 407)	Isolated cleft palate (n = 189)	Isolated cleft lip with/without palate (n = 450)
Carbon monoxide¶					
1st month	0.79 (0.59, 1.05)	0.92 (0.70, 1.21)	0.86 (0.70, 1.06)	1.12 (0.84, 1.50)	1.09 (0.90, 1.32)
2nd month	1.12 (0.81, 1.55)	1.06 (0.78, 1.43)	0.93 (0.73, 1.17)	1.05 (0.76, 1.45)	0.94 (0.76, 1.17)
3rd month	1.06 (0.78, 1.45)	0.92 (0.69, 1.22)	0.87 (0.70, 1.08)	0.71 (0.52, 0.95)	0.90 (0.74, 1.11)
Ozone#					
1st month	1.16 (0.87, 1.54)	0.76 (0.57, 1.02)	1.02 (0.84, 1.25)	1.09 (0.83, 1.45)	0.89 (0.73, 1.08)
2nd month	0.94 (0.67, 1.31)	0.93 (0.67, 1.30)	1.09 (0.86, 1.38)	0.95 (0.68, 1.32)	1.13 (0.90, 1.40)
3rd month	0.93 (0.70, 1.23)	1.10 (0.84, 1.45)	0.80 (0.66, 0.98)	1.01 (0.76, 1.33)	0.92 (0.76, 1.11)

* Adjusted for the following covariates: maternal ethnicity Hispanic, maternal age (<20, 20–29, 30–34, >35 years), parity (none vs. one or more), season of conception (winter, spring, summer, fall).

† A continuous variable for these log-linear models was created by using mean values for each quartile of exposure.

‡ Per 1 ppm carbon monoxide and per 1 pphm ozone increase.

§ Results are based on 3,000 randomly selected control children.

¶ Carbon monoxide quartile means (ppm), 1st month: 0.80, 1.34, 1.98, 3.35; 2nd month: 0.80, 1.34, 1.94, 3.29; 3rd month: 0.78, 1.31, 1.85, 3.16 (range, 0.09–7.02).

Ozone quartile means (pphm), 1st month: 0.64, 1.52, 2.39, 3.42; 2nd month: 0.64, 1.56, 2.42, 3.49; 3rd month: 0.68, 1.66, 2.49, 3.49 (range, 0.14–9.94).

formations (27). Confounding by other risk factors differentially distributed between these communities and ecologic bias could not be ruled out.

Active and passive smoking may be the exposure most comparable to air pollution in their potential to adversely affect fetal development. Active maternal smoking during pregnancy has been associated with a number of birth defects including ventricular septal defects and orofacial clefts (28–36). Prenatal exposure of the human fetus to tobacco smoke through maternal passive smoking has been linked to low birth weight (37). While teratogenicity of sidestream smoke has not been clearly demonstrated in humans, researchers have reported evidence of an unfavorable osteopathic effect of sidestream smoke on fetal development in rats (38).

Our results suggest that certain fetal heart phenotypes may be susceptible to the adverse effects of two ambient pollutants, carbon monoxide and ozone. One potential etiologic pathway may include the neural crest cell population. Normal migration and differentiation of neural crest cells are important for heart development (20). Furthermore, neural crest cells are particularly sensitive to toxic insults and respond by undergoing apoptosis, in part because they lack antioxidative stress proteins (12, 39, 40). Ozone is a very reactive molecule and a strong oxidizing agent that can generate superoxides, hydrogen peroxide, and hydroxyl radicals (41); that is, it contributes to oxidative stress.

Kavlock et al. (15) found that environmentally high exposure to ozone (>1.26 ppm) during organogenesis was embryocidal in rats, resulting in largely increased resorption of fetuses; high ozone levels also reduced skeletal ossification but showed no other obvious teratogenic effects. At lower exposure levels, ozone was observed to interact synergistically with the teratogen salicylate, enhancing fetotoxic effects in the exposed rats possibly by interfering with detoxification of the teratogen or induction of oxidative stress and vitamin E deficiency in the mother (15). Exposing rats for 1–4 days to ozone at 0.4 ppm lowered their serum retinol concentrations by about 85 percent (42), and vitamin A deprivation during development is known to cause numerous congenital defects (43). Ozone prolonged the elimination time of xenobiotics in the lungs of several animals (44), and, while enzyme levels increased in the lung following ozone exposure, liver antioxidant enzymes (superoxide dismutase and glutathione peroxidase) were concomitantly depressed (45). Thus, action of toxic compounds in the atmosphere coinciding with increased ambient ozone formation could be enhanced.

In experimental systems, carbon monoxide has been demonstrated to 1) decrease metabolization of xenobiotics such as benzo-[*a*]-pyrene (13); 2) interfere with metabolic and transport functions of the placenta (13); 3) have a toxic effect on the developing nervous system of rats (13); 4) produce minor skeletal malformations in mice and rabbits at relatively high doses (13); and 5) at lower doses, cause a number of malformations in a dose-dependent and synergistic manner in mice deficient in protein intake during pregnancy (46).

We observed an increased risk of several cardiac defects for second-month carbon monoxide and ozone exposures; thus, the timing of exposures is consistent with cardiac development. However, we also found a reduced risk associated with increased exposures in the third month. This observation might suggest a differential loss of certain affected pregnancies not captured by the CBDMP and may be comparable to increased fetal resorption rates observed in animal exposure studies (14). For chromosomal defects, which manifest at conception, we observed a negative association with carbon monoxide for all 3 months of the first trimester, which may suggest that these fetuses are vulnerable and more likely to die when exposed to carbon monoxide. Ascertainment bias due to prenatal diagnosis as well as selective abortion of fetuses with chromosomal defects cannot be ruled out. These speculations cannot be addressed without outcome information on all conceptions.

A large percentage of carbon monoxide, nitrogen dioxide, and the fine components of PM_{10} in the metropolitan area of southern California is produced by the same vehicular sources, and these pollutants accumulate when trapped over the city by inversion layers, especially during the colder seasons. Ozone is a secondary pollutant generated in the troposphere from the precursors nitrogen dioxide and hydrocarbons, and it follows the opposite seasonal pattern. High levels of carbon monoxide during the winter are related to average wind speed affecting dilution and dispersion of emissions, while low temperatures reduce surface vertical mixing and cause near-surface inversions to be stronger and last longer; high levels of ozone during the summer are due to the contributions of sunlight to ozone production (47). Thus, as expected, Pearson's correlation coefficients (r) for monthly air-pollutant averages during the first trimester of pregnancy showed that, for the population studied, carbon monoxide was most strongly correlated with nitrogen dioxide ($r = 0.73$), less strongly with PM_{10} ($r = 0.32$), and negatively correlated with ozone ($r = -0.72$). Furthermore, sharp carbon monoxide gradients can occur near sources such as areas with a high vehicle density, contributing to a nonhomogeneous spatial distribution of carbon monoxide in close proximity to sources such as freeways. Because of prevailing onshore wind patterns, ozone shows a west-east gradient in the Southern California Air Basin, with higher levels in the eastern and inland areas. If variations in exposure levels were mostly attributable to seasonal and not regional differences in air pollution, risk factors would also have to vary seasonally to confound the relation we observed with air pollution. However, while confounding by unmeasured seasonal factors is possible, we found that our effect estimates were stable or even strengthened when our models included a term for season of conception.

We were unable to evaluate several potential risk factors for birth defects, including maternal smoking, occupational exposures, vitamin supplement use, diet, and obesity, because they are not adequately reported on California birth certificates. However, if these factors vary seasonally and/or are correlated with socioeconomic status, we may have indirectly adjusted for them to some extent by including season of conception, maternal education, and race/ethnicity in our models.

Estimating individual average exposures during specific gestational months by relying on the ambient air monitoring station closest to the maternal residence at delivery may have resulted in exposure misclassification. Particulate measuring stations were on average located farther away from residences and may have provided the least accurate surrogate measures for personal exposure. Potential sources of exposure misclassification for all pollutants include the following: 1) residential addresses reported on birth certificates might be more indicative of the last than the first months of pregnancy (48) and 2), additional exposure misclassification might have occurred if mothers spent substantial amounts of time during pregnancy outside their residential air monitoring district, such as while working or in microenvironments with higher or lower concentrations of specific pollutants; one such high-exposure source for carbon monoxide is in a vehicle while commuting (49). In addition, differences between outdoor and indoor pollutant levels, and thus personal exposures, depend on residential air exchange rates, physical activity, and time spent at home and may have further contributed to exposure misclassification. These errors are assumed to be nondifferential with respect to case or control status. Thus, we assume that such errors would have underestimated the effects. In fact, a recent study showed that when area-wide measures of exposure to air pollution, such as those obtained from fixed-site monitoring stations, are used as proxies for personal exposures, estimates of pollutant effects are generally smaller than those based on exposure levels determined by personal sampling (50).

In conclusion, our results suggest that, in southern California, exposure to increased levels of ambient carbon monoxide during pregnancy may contribute to the occurrence of ventricular septal defects and exposure to increased levels of ozone may elevate the risk of aortic artery and valve defects, and possibly also of pulmonary artery and valve anomalies and of conotruncal defects. While our results for cardiac defects are supported by the specificity of the embryologic and exposure timing and some evidence from animal data, these initial findings need to be confirmed by further studies.

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