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Original Contribution

Ambient Air Pollution and Cardiovascular Malformations in Atlanta, Georgia, 1986–2003

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Associations between ambient air pollution levels during weeks 3–7 of pregnancy and risks of cardiovascular malformations were investigated among the cohort of pregnancies reaching at least 20 weeks' gestation that were conceived during January 1, 1986–March 12, 2003, in Atlanta, Georgia. Surveillance records obtained from the Metropolitan Atlanta Congenital Defects Program, which conducts active, population-based surveillance on this cohort, were reviewed to classify cardiovascular malformations. Ambient 8-hour maximum ozone and 24-hour average carbon monoxide, nitrogen dioxide, particulate matter with an average aerodynamic diameter of <10 μm (PM_{10}), and sulfur dioxide measurements were obtained from centrally located stationary monitors. Temporal associations between these pollutants and daily risks of secundum atrial septal defect, aortic coarctation, hypoplastic left heart syndrome, patent ductus arteriosus, valvar pulmonary stenosis, tetralogy of Fallot, transposition of the great arteries, muscular ventricular septal defect, perimembranous ventricular septal defect, conotruncal defects, left ventricular outflow tract defect, and right ventricular outflow defect were modeled by using Poisson generalized linear models. A statistically significant association was observed between PM_{10} and patent ductus arteriosus (for an interquartile range increase in PM_{10} levels, risk ratio $= 1.60$, 95% confidence interval: 1.11, 2.31). Of the 60 associations examined in the primary analysis, no other significant associations were observed.

air pollution; heart defects, congenital

Abbreviations: CI, confidence interval; MACDP, Metropolitan Atlanta Congenital Defects Program; $PM_{10,}$, particulate matter with an average aerodynamic diameter of <10 μm; RR, risk ratio.

A growing body of epidemiologic evidence suggests associations between ambient air pollution and adverse pregnancy outcomes (1–6). Associations between air pollution levels during pregnancy and risks of cardiovascular malformations among the offspring were investigated in 2 previous population-based case-control studies (7, 8). In these studies, cardiovascular malformations were classified by using preexisting surveillance database codes, and analyses were based on contrasts in ambient pollution levels over space and time.

In the first study, conducted in southern California, investigators reported an association between ambient carbon monoxide levels and risk of ventricular septal defects (fourth quartile vs. first quartile, odds ratio $= 2.95$, 95% confidence interval (CI): 1.44, 6.05). Elevated risks of aortic artery and valve defects, pulmonary artery and valve defects, and conotruncal defects with increasing ambient ozone levels were also reported (7). The second investigation, conducted in Texas, did not corroborate the southern California findings, although a suggestive association between ozone and pulmonary artery and valve defects was observed. The Texas investigators reported positive associations for carbon monoxide and tetralogy of Fallot, particulate matter with an average aerodynamic diameter of <10 μm (PM_{10}) and atrial septal defects, and sulfur dioxide and ventricular septal defects (8).

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Table 1. Cardiovascular Malformation Outcome Groups, Number of Cases,[a] and Outcome Group Definitions

Outcome Group	No. of Cases	Definition
Atrial septal defect, secundum	379	Includes secundum-type atrial septal defect.
Coarctation of the aorta	275	Includes coarctation of the aorta, aortic arch hypoplasia, and interrupted aortic arch type A.
Hypoplastic left heart syndrome	175	Includes hypoplastic left heart syndrome with or without ventricular septal defect.
Patent ductus arteriosus	219	Includes term infants (≥36 weeks' gestation) with patent ductus arteriosus persisting for ≥6 weeks following delivery. Infants were excluded if the patent ductus arteriosus was an obligatory shunt lesion or if patency was maintained by prostaglandin infusion.
Pulmonary stenosis, valvar	312	Includes valvar and unspecified pulmonary stenosis, as well as dysplastic pulmonary valve.
Tetralogy of Fallot	299	Includes typical tetralogy of Fallot, tetralogy of Fallot with absent pulmonary valve, pulmonary atresia with ventricular septal defect, pulmonary atresia with major aortopulmonary collateral arteries, and tetralogy of Fallot-type double-outlet right ventricle.
Transposition of the great arteries	165	Includes all types of transposition with concordant atrioventricular connections and discordant ventricular arterial connections, with or without ventricular septal defect or left ventricular outflow tract obstruction. Also includes double-outlet right ventricle with malpositioned great arteries.
Ventricular septal defect, muscular	1,108	Includes muscular-type ventricular septal defect.
Ventricular septal defect, perimembranous	546	Includes perimembranous-type ventricular septal defect.
Conotruncal defect[b]	661	Includes all cardiovascular malformations in the "Tetralogy of Fallot" and "Transposition of the great arteries" outcome groups. Also includes aortopulmonary window defect, all other double-outlet right-ventricle variants, interrupted aortic arch type B, unspecified interrupted aortic arch, vascular rings, and subarterial-type ventricular septal defect.
Left ventricular outflow tract defect[b]	558	Includes all cardiovascular malformations in the "Coarctation of the aorta" and "Hypoplastic left heart syndrome" outcome groups. Also includes stenosis and atresia of the aortic valve and isolated bicuspid aortic valve.
Right ventricular outflow tract defect[b]	421	Includes all cardiovascular malformations in the "Pulmonary stenosis, valvar" outcome group. Also includes pulmonary valve atresia with intact ventricular septum, tricuspid valve atresia, double-chambered right ventricle, and isolated supravalvar pulmonary artery stenosis.

[a] Number of cases identified among the cohort of pregnancies reaching at least 20 weeks' gestation in Atlanta, Georgia, with an estimated date of conception during January 1, 1986–March 12, 2003.
[b] Aggregate grouping of cardiovascular malformations.

We conducted a retrospective cohort study in Atlanta, Georgia, to explore temporal associations between ambient air pollution levels during pregnancy and risks of cardiovascular malformations. We did not closely replicate the methodologies of the previous studies. In addition to the retrospective cohort design and the temporal analytical approach, we reviewed and reclassified each surveillance record using a modified version of the International Pediatric and Congenital Cardiac Code implemented in the Society of Thoracic Surgeons Congenital Heart Surgery Database (9–13). This activity permitted classification of cardiovascular malformations according to embryologic (rather than only anatomic) considerations.

MATERIALS AND METHODS

Study population

Vital records for the cohort of liveborn and stillborn infants of at least 20 weeks' gestation whose mothers resided in 1 of 5 central Atlanta counties at delivery were obtained from the Office of Health Information and Policy, Georgia Division of Public Health. The records of infants with an indication of a cardiovascular malformation were obtained from the Metropolitan Atlanta Congenital Defects Program (MACDP), which conducts active, population-based birth defects surveillance on the cohort of pregnancies reaching at least 20 weeks' gestation to mothers residing in 1 of 5 central Atlanta counties at delivery/termination (14). MACDP ascertains livebirths, stillbirths, and elective terminations with major structural defects, chromosomal abnormalities, and clinical syndromes diagnosed by the age of 6 years. When available, details from echocardiography, catheterization, and surgical reports are abstracted; general pregnancy information, such as gestational age and birth weight, is also collected.

Pregnancies with an estimated date of conception during January 1, 1986–March 12, 2003, were included in the analysis. For each conception date, we estimated the number of pregnancies with a cardiovascular malformation (numerator) and total pregnancies (denominator). Approximately 0.3% of pregnancies with cardiovascular malformations and 1.9% of total pregnancies were excluded because of missing or implausible gestational age information (defined as <20 weeks or >44 weeks). For each pregnancy, we estimated the date of conception (assuming that conception

Table 2. Prevalence[a] of Cardiovascular Malformations, by Season and Year of Conception, for the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003

	No. of Cases	Prevalence,[a] by Season of Conception				Prevalence,[a] by Year of Conception			Overall Prevalence[a]
		March–May	June–August	September–November	December–February	1986–1991	1992–1997	1998–2003	
Atrial septal defect, secundum	379	4.2	5.4	5.9	5.6	2.8	4.7	7.9	5.3
Coarctation of the aorta	275	3.6	4.0	3.1	4.6	3.9	3.8	3.8	3.8
Hypoplastic left heart syndrome	175	2.0	2.2	3.1	2.4	2.9	2.3	2.3	2.5
Patent ductus arteriosus	219	2.8	3.1	2.9	3.5	3.6	3.1	2.7	3.1
Pulmonary stenosis, valvar	312	3.6	4.6	4.8	4.4	2.7	4.6	5.4	4.4
Tetralogy of Fallot	299	4.4	3.8	4.0	4.5	4.2	4.0	4.3	4.2
Transposition of the great arteries	165	2.3	2.2	2.2	2.5	2.2	2.2	2.5	2.3
Ventricular septal defect, muscular	1,108	14.1	14.8	17.1	15.8	5.3	14.3	24.9	15.5
Ventricular septal defect, perimembranous	546	6.6	7.8	8.4	7.7	4.8	8.1	9.5	7.6
Conotruncal defect[b]	661	9.1	8.3	9.1	10.4	8.4	9.0	10.2	9.2
Left ventricular outflow tract defect[b]	558	6.4	7.5	8.6	8.7	7.9	7.6	7.9	7.8
Right ventricular outflow tract defect[b]	421	5.0	6.2	6.1	6.2	3.9	6.9	6.5	5.9

[a] Prevalence per 10,000 pregnancies reaching at least 20 weeks' gestation.
[b] Aggregate grouping of cardiovascular malformations.

occurred 14 days after the last menstrual period date) using vital records data. Unfortunately, these estimates were unreliable; for 30% of pregnancies, the last menstrual period date was on the 15th of the month. When we subtracted the clinical gestational age estimate from the birth date, too many last menstrual period dates fell between the 12th and 18th of the month.

To compensate for this data quality limitation, we used gestational age estimates from MACDP surveillance records (which are obtained from medical chart review and are frequently based on ultrasound measurements) to estimate conception dates for pregnancies with cardiovascular malformations, because day-of-month patterns were not evident among these estimates. For the denominators, we modeled the daily count of conceptions. We calculated the average daily number of conceptions for each month using vital records information. We then created a daily time-series data set, in which each day was assigned its monthly average, and fit a cubic spline with 6 knots per year to it. The predicted values from this model were used as the daily estimates of conceptions ($n = 715{,}500$ pregnancies).

Cardiovascular malformation outcome groups

Each MACDP surveillance record with a diagnosis of a cardiovascular malformation was reviewed by a pediatric cardiologist and classified by using the Society of Thoracic Surgeons Congenital Heart Surgery Database, version 2.30, nomenclature (11–13, 15). This nomenclature is specific to cardiovascular malformations and is more detailed than what is typically used in birth defects surveillance (16–18). We classified infants with isolated transient newborn cardiac conditions (e.g., patent foramen ovale) as physiologically normal, and we placed infants with more than 1 cardiovascular malformation in multiple outcome groups only when these malformations were thought to be embryologically independent; otherwise, we coded only the major cardiovascular malformation. Further details about this activity are available (12).

For our analyses, we excluded infants who had normal cardiac physiology and those with identified trisomies, evidence of heterotaxy syndrome, and abnormal cardiac looping. Results are presented for 12 outcome groups; 3 of these are aggregate groupings of cardiovascular malformations (Table 1).

Ambient air quality data

Ambient air quality measurements of daily 8-hour maximum ozone and 24-hour average carbon monoxide, nitrogen dioxide, PM_{10}, and sulfur dioxide were obtained from the US Environmental Protection Agency Air Quality System, Georgia Department of Natural Resources, and the Metro Atlanta Index. For each pollutant, we selected 1 central monitoring station for use in analyses. When central station measurements of carbon monoxide, nitrogen dioxide, and sulfur dioxide were missing, pollution levels at the central station were modeled by using measurements from other stations. The central station for ozone did not operate during November–February. During 1993–2003, wintertime ozone levels were modeled by using ozone measurements from a nearby monitor, with the model developed by use of data during the later time period when wintertime ozone levels were available. During 1986–1992, wintertime ozone levels were modeled by using maximum temperature and 1-hour maximum nitrogen dioxide measurements from a nearby monitor. Measurements of PM_{10} were available

Table 3. Interquartile Range and Mean Values, by Season and Year of Conception, for the Weighted 5-Week Air Pollution Metric[a] Assigned to the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003

	8-Hour Ozone, ppb[b,c]	24-Hour PM_{10}, $\mu g/m^3$ [c,d]	24-Hour Nitrogen Dioxide, ppb[c]	24-Hour Carbon Monoxide, ppm[c]	24-Hour Sulfur Dioxide, ppb[c]
Interquartile range	29.9	14.2	5.7	0.3	4.0
Mean value, by season of conception					
March–May	54.6	36.0	24.2	0.6	5.4
June–August	56.5	38.7	22.6	0.8	5.4
September–November	25.4	31.2	26.9	0.9	6.9
December–February	29.2	27.3	26.5	0.7	7.1
Mean value, by year of conception					
1986–1991	43.3	43.2	28.0	0.7	8.7
1992–1997	39.8	30.0	24.3	0.8	5.5
1998–2003	41.2	25.8	22.5	0.7	4.0

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.

[a] The air pollution metric is a 5-week weighted average of daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy. Relative weights are 0.7, 0.9, and 1.0 for pollution levels during the first and last week, the second and fourth week, and the middle week of the window, respectively.

[b] The central station for ozone did not operate during winter months (November–February).

[c] Daily central monitoring station measurements available: 67% (4,251 of 6,315 days) for ozone, 41% (2,563 of 6,315 days) for PM_{10}, 90% (5,670 of 6,315 days) for nitrogen dioxide, 92% (5,804 of 6,315 days) for carbon monoxide, and 94% (5,966 of 6,315 days) for sulfur dioxide. When feasible, missing daily measurements were modeled: 33% (2,064 of 6,315 days) for ozone, 59% (3,735 of 6,315 days) for PM_{10}, 10% (609 of 6,315 days) for nitrogen dioxide, 6% (388 of 6,315 days) for carbon monoxide, and 5% (311 of 6,315 days) for sulfur dioxide.

[d] PM_{10} was measured every sixth day during 1986–1992, Sunday–Thursday during 1993–1995, and daily during 1996–2003. The location of the PM_{10} central monitoring station changed on January 1, 1993, and on January 1, 1998; on January 1, 1998, the measurement method changed from the federal reference method to tapered element oscillating microbalance.

every sixth day during 1986–1992, Sunday–Thursday during 1993–1995, and daily during 1996–2003; linear interpolation between measurements was used to estimate missing PM_{10} levels. The location of the PM_{10} central monitoring station changed on January 1, 1993, and on January 1, 1998; on January 1, 1998, the measurement method changed from the federal reference method to the tapered element oscillating microbalance method.

Statistical analyses

For each conception date (January 1, 1986–March 12, 2003), we estimated the number of pregnancies with a particular cardiovascular malformation (numerator) and total pregnancies (denominator). All pregnancies on a particular conception date were assigned the same pollutant metric, which was a weighted average of the 35 daily ambient air pollution measurements during weeks 3–7 of pregnancy (a period when the 4 chambers, inflow tract, and outflow tract of the heart develop (19)). Relative weights were 0.7 for measurements during weeks 3 and 7, 0.9 for measurements during weeks 4 and 6, and 1.0 for measurements during week 5. We chose this a priori weighting scheme, which emphasizes pollution levels during the center of the window, because of uncertainty in the date of conception estimates.

We then created 52 strata representing the week-of-year as follows: across all calendar years we grouped January 1–January 7 as the first week of the year, January 8–January 14 as the second week of the year, and so on. We included February 29, when present, in the ninth week of the year (February 26–March 4). The 52nd week of the year was 8 days long (December 24–December 31).

We modeled temporal associations between ambient air pollution and daily risks of cardiovascular malformations using Poisson generalized linear models with a log link and scaled variance estimates. We modeled the pollution metric as a continuous variable and used the natural logarithm of total conceptions as the offset. We included indicator variables for the 52 strata representing week-of-year to control for potential confounding by factors with seasonal variation, and we included a cubic spline for day of follow-up with 1 knot per year to control for long-term trends. All risk ratios and confidence intervals corresponded to an interquartile range increase in the ambient pollutant metric.

Table 4. Spearman's Partial Correlation Coefficients for the Weighted 5-Week Air Pollution Metric Assigned to the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	8-Hour Ozone, ppb	24-Hour PM_{10}, $\mu g/m^3$	24-Hour Nitrogen Dioxide, ppb	24-Hour Carbon Monoxide, ppm	24-Hour Sulfur Dioxide, ppb
8-Hour ozone, ppb	1.00				
24-Hour PM_{10}, $\mu g/m^3$	0.49***	1.00			
24-Hour nitrogen dioxide, ppb	0.45***	0.46***	1.00		
24-Hour carbon monoxide, ppm	0.07***	0.32***	0.41***	1.00	
24-Hour sulfur dioxide, ppb	0.30***	0.41***	0.39***	0.23***	1.00

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.
*** $P < 0.001$.
[a] Linear regression models containing week-of-year indicator variables and a cubic spline for day of follow-up with 1 knot per year were used to predict the daily pollution metrics. The pairwise Spearman partial correlation coefficients were estimated by using the residuals from these models. The air pollution metric is a weighted average of the 35 daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy.

Models were created by using R statistical software, version 2.5.0 (20).

We performed several sensitivity analyses. In one sensitivity analysis, we relaxed the seasonal and long-term temporal controls by replacing the week-of-year indicator variables with a cubic spline for day-of-year that had 3 knots; instead of including yearly knots in the cubic spline for day of follow-up, we placed knots once every 3 years.

Table 5. Risk Ratios and 95% Confidence Intervals for Associations Between the Weighted 5-Week Air Pollution Metric and Cardiovascular Malformations Among the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	No. of Cases	8-Hour Ozone, ppb		24-Hour PM_{10}, $\mu g/m^3$		24-Hour Nitrogen Dioxide, ppb		24-Hour Carbon Monoxide, ppm		24-Hour Sulfur Dioxide, ppb	
		Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Atrial septal defect, secundum	379	1.16	0.67, 2.00	1.12	0.82, 1.53	1.15	0.92, 1.43	0.92	0.74, 1.15	1.00	0.72, 1.38
Coarctation of the aorta	275	1.15	0.65, 2.06	1.15	0.84, 1.58	1.11	0.87, 1.41	0.99	0.79, 1.24	1.04	0.75, 1.43
Hypoplastic left heart syndrome	175	0.82	0.37, 1.84	0.89	0.60, 1.31	0.91	0.66, 1.24	0.80	0.60, 1.06	0.77	0.50, 1.18
Patent ductus arteriosus	219	1.39	0.72, 2.68	1.60	1.11, 2.31	1.27	0.96, 1.70	1.18	0.92, 1.51	1.22	0.86, 1.74
Pulmonary stenosis, valvar	312	0.97	0.53, 1.75	0.87	0.63, 1.21	1.01	0.80, 1.28	1.06	0.86, 1.32	0.70	0.49, 1.00
Tetralogy of Fallot	299	1.09	0.59, 2.00	0.88	0.65, 1.20	0.94	0.74, 1.20	1.13	0.91, 1.40	0.85	0.61, 1.17
Transposition of the great arteries	165	1.29	0.58, 2.85	1.12	0.74, 1.72	0.80	0.57, 1.11	0.94	0.68, 1.30	1.13	0.75, 1.71
Ventricular septal defect, muscular	1,108	1.08	0.77, 1.50	1.01	0.83, 1.23	1.09	0.96, 1.24	0.99	0.85, 1.14	0.95	0.77, 1.17
Ventricular septal defect, perimembranous	546	1.06	0.67, 1.68	0.94	0.73, 1.22	1.12	0.94, 1.33	0.96	0.81, 1.14	0.99	0.76, 1.28
Conotruncal defect	661	1.22	0.81, 1.85	0.99	0.80, 1.22	0.95	0.81, 1.12	1.04	0.89, 1.21	1.06	0.86, 1.31
Left ventricular outflow tract defect	558	1.09	0.70, 1.68	1.03	0.83, 1.29	1.01	0.85, 1.20	0.97	0.82, 1.13	0.97	0.76, 1.22
Right ventricular outflow tract defect	421	0.73	0.44, 1.22	0.85	0.64, 1.12	1.02	0.84, 1.25	1.16	0.96, 1.40	0.74	0.55, 1.00

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.
[a] Risk ratios and 95% confidence intervals correspond to an increase in the interquartile range of the 5-week air pollutant metric (a weighted average of the 35 daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy). The interquartile ranges were 29.9 ppb for ozone, 14.2 $\mu g/m^3$ for PM_{10}, 5.7 ppb for nitrogen dioxide, 0.30 ppm for carbon monoxide, and 4.0 ppb for sulfur dioxide.

Table 6. Sensitivity Analysis With Less Stringent Control of Seasonal and Long-Term Temporal Variation, With Risk Ratios and 95% Confidence Intervals for Associations Between the Weighted 5-Week Air Pollution Metric and Cardiovascular Malformations Among the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	No. of Cases	8-Hour Ozone, ppb		24-Hour PM_{10}, $\mu g/m^3$		24-Hour Nitrogen Dioxide, ppb		24-Hour Carbon Monoxide, ppm		24-Hour Sulfur Dioxide, ppb	
		Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Atrial septal defect, secundum	379	1.25	0.74, 2.09	1.12	0.82, 1.52	1.16	0.94, 1.43	0.97	0.80, 1.18	1.05	0.77, 1.43
Coarctation of the aorta	275	1.21	0.68, 2.16	1.21	0.90, 1.63	1.03	0.82, 1.30	1.00	0.82, 1.22	1.02	0.75, 1.40
Hypoplastic left heart syndrome	175	1.37	0.63, 3.00	1.12	0.75, 1.66	0.92	0.68, 1.25	0.93	0.73, 1.20	0.84	0.55, 1.27
Patent ductus arteriosus	219	1.26	0.65, 2.43	1.40	1.01, 1.95	1.40	1.07, 1.83	1.19	0.96, 1.47	1.27	0.90, 1.79
Pulmonary stenosis, valvar	312	1.23	0.70, 2.15	1.00	0.73, 1.37	1.07	0.86, 1.33	1.09	0.90, 1.32	0.80	0.57, 1.13
Tetralogy of Fallot	299	1.24	0.72, 2.14	0.98	0.73, 1.30	1.02	0.82, 1.26	1.10	0.92, 1.30	0.82	0.61, 1.10
Transposition of the great arteries	165	1.70	0.83, 3.48	1.01	0.69, 1.49	0.77	0.58, 1.03	0.94	0.72, 1.23	0.98	0.67, 1.44
Ventricular septal defect, muscular	1,108	1.17	0.87, 1.56	1.02	0.85, 1.23	1.05	0.94, 1.18	1.01	0.90, 1.13	0.93	0.77, 1.13
Ventricular septal defect, perimembranous	546	1.11	0.73, 1.69	0.92	0.72, 1.17	1.05	0.89, 1.23	1.00	0.86, 1.17	0.98	0.76, 1.25
Conotruncal defect	661	1.34	0.93, 1.93	1.01	0.73, 1.30	1.00	0.87, 1.15	1.05	0.93, 1.19	0.96	0.79, 1.17
Left ventricular outflow tract defect	558	1.37	0.91, 2.06	1.17	0.95, 1.44	0.99	0.84, 1.16	1.02	0.90, 1.17	0.99	0.79, 1.23
Right ventricular outflow tract defect	421	0.94	0.58, 1.52	0.94	0.72, 1.23	1.00	0.83, 1.20	1.16	0.98, 1.36	0.85	0.65, 1.13

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.

[a] Risk ratios and 95% confidence intervals correspond to an increase in the interquartile range of the 5-week air pollutant metric (a weighted average of the 35 daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy). The interquartile ranges were 29.9 ppb for ozone, 14.2 $\mu g/m^3$ for PM_{10}, 5.7 ppb for nitrogen dioxide, 0.30 ppm for carbon monoxide, and 4.0 ppb for sulfur dioxide.

We also investigated the effect of limiting analyses to single gestation pregnancies, limiting analyses to infants with only 1 cardiovascular malformation, using unweighted 5-week pollution metrics, and using unweighted 9-week pollution metrics (the average of measurements during the first 63 days of pregnancy).

RESULTS

Surveillance records of pregnancies reaching 20 weeks' gestation with an estimated date of conception during January 1, 1986–March 12, 2003, indication of a cardiovascular malformation, and no evidence of trisomy were identified ($n = 7{,}102$). Of these, only 4,639 (65%) were deemed to have a cardiovascular malformation following review and classification. Infants with complex malformations involving abnormal cardiac looping ($n = 86$) or heterotaxy syndrome ($n = 96$) were excluded from analysis, irrespective of the other specific cardiovascular lesions that might have been present. From the remaining 4,457 infants, 3,338 (75%) were included in 1 or more of the outcome groups shown in Table 1. Overall, there were 715,500 liveborn and stillborn infants with an estimated date of conception during this period.

The prevalence of cardiovascular malformations, shown in Table 2 by season and year of conception, suggested some seasonal variation across outcome groups. Whereas the observed prevalence of the relatively severe lesions (hypoplastic left heart syndrome, transposition of the great arteries, and tetralogy of Fallot) remained stable over time, the observed prevalence of the less severe lesions (secundum atrial septal defect, valvar pulmonary stenosis, muscular ventricular septal defect, and perimembranous ventricular septal defect) increased markedly.

Descriptive statistics for the air pollution metrics, which are weighted averages of daily ambient pollution measurements during weeks 3–7 of pregnancy, indicated that all pollutants had seasonal variation (Table 3). Levels of PM_{10}, nitrogen dioxide, and sulfur dioxide declined over time. Pairwise Spearman partial correlation coefficients for the pollution metrics are presented in Table 4.

As shown in Table 5, we observed a statistically significant positive association between PM_{10} and patent ductus arteriosus (for an interquartile range increase in PM_{10} levels, risk ratio (RR) = 1.60, 95% CI: 1.11, 2.31). The 95% confidence intervals for all other associations, presented in Table 5, included the null value.

Results from 5 sensitivity analyses are presented in Tables 6–10. We consistently observed positive associations between PM_{10} and patent ductus arteriosus (less stringent seasonal and long-term temporal control, RR = 1.40, 95% CI: 1.01, 1.95; limited to single gestation pregnancies, RR = 1.57, 95% CI: 1.07, 2.28; limited to infants with only 1 cardiovascular malformation, RR = 1.70, 95% CI: 1.12, 2.56; using an unweighted 5-week metric, RR = 1.53, 95%

Table 7. Sensitivity Analysis Limited to Single Gestation Pregnancies, With Risk Ratios and 95% Confidence Intervals for Associations Between the Weighted 5-Week Air Pollution Metric and Cardiovascular Malformations Among the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	No. of Cases	8-Hour Ozone, ppb		24-Hour PM_{10}, $\mu g/m^3$		24-Hour Nitrogen Dioxide, ppb		24-Hour Carbon Monoxide, ppm		24-Hour Sulfur Dioxide, ppb	
		Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Atrial septal defect, secundum	347	1.19	0.67, 2.11	1.10	0.79, 1.51	1.12	0.89, 1.41	0.86	0.68, 1.09	1.02	0.73, 1.43
Coarctation of the aorta	254	1.11	0.61, 2.01	1.24	0.89, 1.72	1.14	0.89, 1.46	1.02	0.81, 1.29	1.09	0.78, 1.53
Hypoplastic left heart syndrome	166	0.92	0.40, 2.11	0.90	0.60, 1.35	0.89	0.65, 1.23	0.79	0.59, 1.06	0.78	0.50, 1.21
Patent ductus arteriosus	215	1.25	0.64, 2.46	1.57	1.07, 2.28	1.23	0.92, 1.65	1.19	0.92, 1.52	1.17	0.81, 1.67
Pulmonary stenosis, valvar	286	0.95	0.51, 1.78	0.87	0.62, 1.23	1.00	0.78, 1.27	1.07	0.85, 1.34	0.73	0.51, 1.05
Tetralogy of Fallot	284	1.04	0.55, 1.96	0.87	0.63, 1.20	0.94	0.73, 1.21	1.15	0.93, 1.44	0.85	0.61, 1.18
Transposition of the great arteries	160	1.15	0.51, 2.60	1.13	0.74, 1.72	0.79	0.56, 1.10	0.91	0.65, 1.27	1.09	0.72, 1.66
Ventricular septal defect, muscular	1,027	1.08	0.76, 1.51	0.99	0.81, 1.22	1.13	0.99, 1.29	1.00	0.86, 1.16	0.94	0.75, 1.17
Ventricular septal defect, perimembranous	514	1.06	0.66, 1.70	0.95	0.72, 1.23	1.11	0.93, 1.33	0.96	0.81, 1.14	0.94	0.72, 1.23
Conotruncal defect	629	1.16	0.76, 1.78	0.98	0.63, 1.20	0.93	0.79, 1.10	1.04	0.89, 1.21	1.03	0.83, 1.28
Left ventricular outflow tract defect	523	1.09	0.70, 1.71	1.08	0.85, 1.35	1.00	0.84, 1.20	0.97	0.82, 1.14	1.00	0.79, 1.27
Right ventricular outflow tract defect	389	0.68	0.40, 1.16	0.83	0.62, 1.12	1.00	0.81, 1.23	1.16	0.96, 1.41	0.76	0.56, 1.03

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.

[a] Risk ratios and 95% confidence intervals correspond to an increase in the interquartile range of the 5-week air pollutant metric (a weighted average of the 35 daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy). The interquartile ranges were 29.9 ppb for ozone, 14.2 $\mu g/m^3$ for PM_{10}, 5.7 ppb for nitrogen dioxide, 0.30 ppm for carbon monoxide, and 4.0 ppb for sulfur dioxide.

CI: 1.02, 2.29; using an unweighted 9-week metric, RR = 1.71, 95% CI: 0.98, 3.00). We observed a positive, statistically significant association between nitrogen dioxide and patent ductus arteriosus in the analysis with less stringent seasonal and long-term temporal control (RR = 1.40, 95% CI: 1.07, 1.83). Using unweighted 9-week pollution metrics, we observed positive, statistically significant associations between nitrogen dioxide and both secundum atrial septal defect (RR = 1.58, 95% CI: 1.02, 2.29) and muscular ventricular septal defect (RR = 1.20, 95% CI: 1.02, 1.41). We also observed negative, statistically significant associations between ozone and right ventricular outflow tract defects in the analysis limited to infants with only 1 cardiovascular malformation (RR = 0.52, 95% CI: 0.29, 0.93) and between sulfur dioxide and right ventricular outflow tract defects in the analysis based on an unweighted 5-week metric (RR = 0.73, 95% CI: 0.54, 0.98).

DISCUSSION

We investigated temporal associations between ambient air pollution levels during weeks 3–7 of pregnancy and risks of cardiovascular malformations. Except for the association between PM_{10} and patent ductus arteriosus, all 95% confidence intervals from the primary analysis were consistent with little or no association. Many confidence intervals, particularly those for ozone, were wide and were therefore compatible with both no effect and a harmful effect of air pollution.

Patent ductus arteriosus was not investigated in the 2 previous studies (7, 8), likely because identification of infants with congenital patent ductus arteriosus is difficult. In our study population, we used restrictive criteria to exclude patent ductus arteriosus in premature or newborn infants and when it occurred as an obligate shunt lesion in the presence of other cardiovascular malformations. Of the 2,273 surveillance records we reviewed that contained a code for patent ductus arteriosus, the records for only 219 infants met these criteria.

We are unaware of experimental animal evidence supporting an association between PM_{10} and patent ductus arteriosus. Analogous epidemiologic evidence comes from Swedish registry data, wherein a positive association was observed between first trimester maternal smoking and risk of patent ductus arteriosus among term infants (21). One plausible biologic mechanism for our result relates to fetal growth and development. Relative to term infants, premature infants have a much higher incidence of patent ductus (22, 23). Associations between reduced fetal growth and maternal smoking (24), environmental tobacco smoke (25), and ambient particulate matter (26, 27) have been observed in epidemiologic studies. If high PM_{10} levels in utero restrict fetal development, this could explain an association between PM_{10} and patent ductus arteriosus among term infants.

Table 8. Sensitivity Analysis Limited to Infants and Fetuses With Only 1 Cardiovascular Malformation, With Risk Ratios and 95% Confidence Intervals for Associations Between the Weighted 5-Week Air Pollution Metric and Cardiovascular Malformations Among the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	No. of Cases	8-Hour Ozone, ppb		24-Hour PM_{10}, $\mu g/m^3$		24-Hour Nitrogen Dioxide, ppb		24-Hour Carbon Monoxide, ppm		24-Hour Sulfur Dioxide, ppb	
		Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Atrial septal defect, secundum	202	0.80	0.36, 1.73	1.03	0.67, 1.57	1.04	0.77, 1.41	1.08	0.80, 1.46	1.16	0.75, 1.79
Coarctation of the aorta	145	1.09	0.51, 2.32	1.16	0.75, 1.79	1.08	0.78, 1.50	1.04	0.76, 1.43	0.89	0.56, 1.39
Hypoplastic left heart syndrome	167	0.80	0.35, 1.82	0.90	0.61, 1.34	0.91	0.66, 1.24	0.83	0.62, 1.10	0.82	0.53, 1.28
Patent ductus arteriosus	171	1.20	0.56, 2.59	1.70	1.12, 2.56	1.31	0.95, 1.81	1.25	0.95, 1.64	1.37	0.92, 2.04
Pulmonary stenosis, valvar	225	0.76	0.37, 1.56	0.88	0.61, 1.27	1.01	0.77, 1.33	1.13	0.88, 1.45	0.74	0.49, 1.11
Tetralogy of Fallot	279	0.96	0.50, 1.81	0.85	0.62, 1.18	0.89	0.69, 1.15	1.17	0.94, 1.46	0.87	0.62, 1.22
Transposition of the great arteries	140	1.28	0.54, 3.03	1.12	0.71, 1.78	0.79	0.55, 1.13	0.93	0.65, 1.31	1.19	0.76, 1.87
Ventricular septal defect, muscular	976	0.90	0.64, 1.28	0.98	0.79, 1.20	1.06	0.92, 1.21	1.00	0.85, 1.16	0.91	0.73, 1.15
Ventricular septal defect, perimembranous	388	1.22	0.71, 2.11	0.93	0.68, 1.26	1.19	0.97, 1.46	0.97	0.79, 1.18	1.08	0.80, 1.47
Conotruncal defect	571	1.12	0.72, 1.76	0.96	0.76, 1.21	0.91	0.76, 1.09	1.07	0.91, 1.27	1.05	0.83, 1.32
Left ventricular outflow tract defect	406	1.00	0.61, 1.66	0.99	0.76, 1.28	0.94	0.77, 1.14	0.97	0.80, 1.16	0.89	0.67, 1.18
Right ventricular outflow tract defect	331	0.52	0.29, 0.93	0.81	0.59, 1.10	1.02	0.81, 1.28	1.23	1.00, 1.51	0.77	0.56, 1.07

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.

[a] Risk ratios and 95% confidence intervals correspond to an increase in the interquartile range of the 5-week air pollutant metric (a weighted average of the 35 daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy). The interquartile ranges were 29.9 ppb for ozone, 14.2 $\mu g/m^3$ for PM_{10}, 5.7 ppb for nitrogen dioxide, 0.30 ppm for carbon monoxide, and 4.0 ppb for sulfur dioxide.

Similar to our study, most results reported in the 2 previous studies were consistent with no association (7, 8). In southern California, investigators reported 4 significant positive associations from 144 models. Twenty-four of these models averaged pollution levels over weeks 5–8 of pregnancy; the 4 positive associations were observed during this window (7). The Texas study investigators observed 3 positive associations from 75 models; air pollution levels were averaged during weeks 3–8 of pregnancy (8). No significant association from the southern California study was replicated in the Texas study.

Because of our review and classification of surveillance records, comparison of results from our study with those from previous studies was difficult. Through our review, we excluded infants with structurally normal hearts and transient newborn conditions; 35% of the records we reviewed were reclassified as ''structurally normal.'' Outcome groups were based on embryologic considerations, and infants with multiple congenital heart defect codes were included in multiple outcome groups only when the malformations were thought to be embryologically independent. Consequently, our outcome groups differed from those used in previous studies (7, 8). For example, in the southern California study (7), an association was observed between carbon monoxide and isolated ventricular septal defects (fourth quartile vs. first quartile, odds ratio = 2.95, 95% CI: 1.44, 6.05). This outcome group incorporated the 4 major types of ventricular septal defects, as well as pulmonary atresia with ventricular septal defect. In our study, we distinguished among the 4 types of ventricular septal defects, because each is thought to develop through unique embryologic mechanisms (28, 29). We analyzed perimembranous and muscular ventricular septal defects as distinct outcome groups, and we included subarterial ventricular septal defects in the conotruncal defects outcome group (Table 1). There were too few inlet ventricular septal defects to permit analysis. We grouped pulmonary atresia with ventricular septal defect, which is the extreme end of the anatomic spectrum of tetralogy of Fallot (30), in the tetralogy of Fallot outcome group. To provide a more direct comparison with the southern California result, we performed a secondary analysis in which we ignored our classifications and defined isolated ventricular septal defect according to the preexisting codes in the MACDP database. Using our primary analytical approach, we observed no evidence for an association between carbon monoxide and isolated ventricular septal defects (RR = 0.98, 95% CI: 0.82, 1.16).

Our analytical approach and exposure assignment methods were also different. Whereas the previous study investigators conducted spatial-temporal analyses using pollution measurements assigned to women on the basis of residential location, we opted for a temporal approach using measurements from centrally located monitors. We implemented a temporal analysis because of our desire to preclude concerns about our study results based on arguments of spatial confounding. We characterized pollution levels using

Table 9. Sensitivity Analysis Based on Unweighted 5-Week Pollution Metrics, With Risk Ratios and 95% Confidence Intervals for Associations Between Air Pollution and Cardiovascular Malformations Among the Cohort of Pregnancies Reaching at least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	No. of Cases	8-Hour Ozone, ppb		24-Hour PM_{10}, $\mu g/m^3$		24-Hour Nitrogen Dioxide, ppb		24-Hour Carbon Monoxide, ppm		24-Hour Sulfur Dioxide, ppb	
		Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Atrial septal defect, secundum	379	1.09	0.62, 1.90	1.09	0.77, 1.54	1.14	0.92, 1.42	0.93	0.75, 1.16	1.00	0.72, 1.38
Coarctation of the aorta	275	1.18	0.66, 2.12	1.19	0.84, 1.68	1.11	0.87, 1.41	0.98	0.79, 1.22	1.04	0.75, 1.44
Hypoplastic left heart syndrome	175	0.78	0.34, 1.77	0.85	0.55, 1.31	0.89	0.65, 1.21	0.82	0.63, 1.08	0.76	0.49, 1.18
Patent ductus arteriosus	219	1.35	0.69, 2.64	1.53	1.02, 2.29	1.26	0.94, 1.69	1.18	0.93, 1.50	1.19	0.84, 1.70
Pulmonary stenosis, valvar	312	0.92	0.50, 1.68	0.83	0.57, 1.19	0.99	0.78, 1.25	1.03	0.84, 1.28	0.71	0.50, 1.01
Tetralogy of Fallot	299	1.08	0.58, 2.01	0.89	0.63, 1.26	0.94	0.73, 1.21	1.15	0.93, 1.41	0.81	0.59, 1.13
Transposition of the great arteries	165	1.26	0.57, 2.82	1.20	0.76, 1.91	0.80	0.57, 1.11	0.99	0.73, 1.35	1.13	0.75, 1.71
Ventricular septal defect, muscular	1,108	1.08	0.77, 1.50	1.05	0.84, 1.30	1.08	0.95, 1.23	0.99	0.86, 1.14	0.95	0.77, 1.17
Ventricular septal defect, perimembranous	546	0.99	0.62, 1.57	0.93	0.70, 1.24	1.11	0.93, 1.32	0.93	0.78, 1.09	0.98	0.76, 1.26
Conotruncal defect	661	1.21	0.79, 1.84	1.01	0.80, 1.28	0.95	0.81, 1.12	1.07	0.93, 1.24	1.05	0.85, 1.30
Left ventricular outflow tract defect	558	1.07	0.69, 1.67	1.04	0.81, 1.33	1.00	0.84, 1.19	0.98	0.84, 1.14	0.96	0.76, 1.22
Right ventricular outflow tract defect	421	0.71	0.43, 1.19	0.80	0.58, 1.09	1.01	0.83, 1.24	1.16	0.97, 1.39	0.73	0.54, 0.98

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.

[a] Risk ratios and 95% confidence intervals correspond to an increase in the interquartile range of the 5-week air pollutant metric (an unweighted average of the 35 daily ambient air pollution levels measured at a central monitor during weeks 3–7 of pregnancy). The interquartile ranges were 29.7 ppb for ozone, 15.4 $\mu g/m^3$ for PM_{10}, 5.7 ppb for nitrogen dioxide, 0.30 ppm for carbon monoxide, and 4.0 ppb for sulfur dioxide.

a centrally located monitor because of practical limitations. Namely, geocoded data were available dating back only to 1994, whereas the central monitor approach allowed us to utilize data back to 1986. Throughout much of follow-up, there were only 2 or 3 monitors for each primary pollutant, and we determined that some monitors were unduly impacted by local sources. We were hesitant to use these measurements, which likely better reflect local conditions than population exposure. The use of 1 central monitor for each pollutant also provided some consistency throughout follow-up; otherwise, modeling assumptions would have been needed to account for changes in the number and location of monitoring stations. For the PM_{10} analyses, we relied on such assumptions, and cubic spline knots were placed on the dates when the monitor location and measurement method changed. To examine the effect of these assumptions, we stratified the data according to measurement method (federal reference method: 1986–1997; tapered element oscillating microbalance: 1998–2003). For PM_{10} and patent ductus arteriosus, we observed a strong association during 1986–1997 (RR = 1.89, 95% CI: 1.26, 2.84) and no association during 1998–2003 (RR = 0.78, 95% CI: 0.28, 2.04). Perhaps the strong association observed during 1986–1997 was attributable to average PM_{10} levels being 42% higher during this period of follow-up (Table 3).

A limitation of our study, also a limitation in previous studies (7, 8), was that results were based on the cohort of pregnancies reaching at least 20 weeks' gestation. Given that our gestational window of interest spanned weeks 3–7 of pregnancy, we would have preferred our cohort to consist of all pregnancies at week 3. The consequence of this limitation might depend on the causal effect of air pollution on cardiovascular malformations. For example, atrioventricular septal defect, Ebstein's anomaly, and tricuspid valve dysplasia can all cause intrauterine congestive heart failure, increasing the risk of intrauterine fetal death (31). If air pollution were to increase the risk of these malformations, in turn increasing the risk of fetal loss before week 20, then our study would have been unable to detect this harmful effect of pollution.

Measurement error or its discrete counterpart, misclassification, which was present in the air quality, vital records, and surveillance data, was another limitation in our study as in previous studies (7, 8). Our use of ambient air pollution measurements from stationary monitors as proxies for personal exposure was likely the largest component of measurement error. If this measurement error was nondifferential, a bias toward the null could explain some null results (32). If the measurement error was differential, for example, if the magnitude of measurement error varied according to meteorologic conditions, then risk ratio estimates may have been biased toward, away from, or across the null. We did not observe broad patterns of consistently positive or negative risk ratios suggesting the possibility of differential measurement error, although differential measurement error may have biased some results.

Table 10. Sensitivity Analysis Based on Unweighted 9-Week Pollution Metrics, With Risk Ratios and 95% Confidence Intervals for Associations Between Air Pollution and Cardiovascular Malformations Among the Cohort of Pregnancies Reaching at Least 20 Weeks' Gestation in Atlanta, Georgia, With an Estimated Date of Conception During January 1, 1986–March 12, 2003[a]

	No. of Cases	8-Hour Ozone, ppb		24-Hour PM_{10}, $\mu g/m^3$		24-Hour Nitrogen Dioxide, ppb		24-Hour Carbon Monoxide, ppm		24-Hour Sulfur Dioxide, ppb	
		Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval	Risk Ratio	95% Confidence Interval
Atrial septal defect, secundum	379	1.36	0.70, 2.65	1.19	0.73, 1.94	1.58	1.19, 2.09	1.08	0.85, 1.37	1.04	0.70, 1.56
Coarctation of the aorta	275	1.29	0.64, 2.57	1.32	0.82, 2.12	1.19	0.88, 1.61	0.93	0.73, 1.20	1.00	0.65, 1.52
Hypoplastic left heart syndrome	175	1.16	0.44, 3.03	1.03	0.58, 1.83	1.00	0.68, 1.47	0.80	0.59, 1.09	0.80	0.47, 1.36
Patent ductus arteriosus	219	1.38	0.61, 3.10	1.71	0.98, 3.00	1.21	0.84, 1.74	1.09	0.83, 1.43	1.20	0.76, 1.89
Pulmonary stenosis, valvar	312	1.01	0.50, 2.04	0.99	0.59, 1.65	1.04	0.78, 1.39	1.07	0.84, 1.37	0.73	0.47, 1.14
Tetralogy of Fallot	299	1.03	0.50, 2.11	1.01	0.64, 1.59	0.98	0.72, 1.33	1.22	0.97, 1.54	0.78	0.51, 1.17
Transposition of the great arteries	165	1.88	0.72, 4.94	1.68	0.90, 3.17	0.77	0.51, 1.15	0.93	0.65, 1.32	1.24	0.74, 2.09
Ventricular septal defect, muscular	1,108	1.11	0.74, 1.65	1.18	0.88, 1.59	1.20	1.02, 1.41	0.98	0.83, 1.15	1.00	0.76, 1.30
Ventricular septal defect, perimembranous	546	1.00	0.58, 1.73	0.82	0.55, 1.21	1.12	0.90, 1.40	0.94	0.78, 1.13	0.88	0.64, 1.22
Conotruncal defect	661	1.22	0.75, 2.00	1.19	0.87, 1.64	0.97	0.79, 1.19	1.10	0.93, 1.30	1.16	0.89, 1.52
Left ventricular outflow tract defect	558	1.19	0.71, 1.99	1.21	0.87, 1.70	1.06	0.85, 1.31	0.94	0.79, 1.12	0.98	0.73, 1.33
Right ventricular outflow tract defect	421	0.88	0.48, 1.61	1.00	0.65, 1.53	1.02	0.80, 1.31	1.17	0.95, 1.45	0.82	0.57, 1.18

Abbreviation: PM_{10}, particulate matter with an average aerodynamic diameter of <10 μm.

[a] Risk ratios and 95% confidence intervals correspond to an increase in the interquartile range of the 9-week air pollutant metric (an unweighted average of the 63 daily ambient air pollution levels measured at a central monitor during weeks 1–9 of pregnancy). The interquartile ranges were 27.4 ppb for ozone, 15.1 $\mu g/m^3$ for PM_{10}, 5.3 ppb for nitrogen dioxide, 0.28 ppm for carbon monoxide, and 3.9 ppb for sulfur dioxide.

Misclassification in the vital records data was evident by the strong day-of-month pattern observed in the date-of-conception estimates. Although a statistical model was created to remove this day-of-month pattern, uncertainty in the estimates remained. The date-of-conception estimates from MACDP surveillance records, although lacking an obvious day-of-month pattern, likewise had uncertainty. Although we selected our exposure window to coincide with the period of cardiac morphogenesis, it is possible that exposures earlier or later in pregnancy could have affected the development of certain malformations (33). Some results were sensitive to the window definition; for pollution levels during the first 9 weeks of pregnancy, we observed positive, statistically significant associations between nitrogen dioxide and both secundum atrial septal defect and muscular ventricular septal defect. Although the point estimates for these 2 associations were elevated in our primary analysis, neither was statistically significant (Table 5).

Ours is the third epidemiologic study of air pollution and cardiovascular malformations reported to date (7, 8). Results from these 3 studies do not seem consistent. This inconsistency could be due to the absence of true associations between ambient air pollution and risks of cardiovascular malformations; it also could be due to differences in populations, pollution levels, outcome definitions, or analytical approaches. If ambient air pollution levels do cause cardiovascular malformations, then the lack of consistency of results might be due to issues relating to statistical power and measurement error. Although our study population was large, we nevertheless would have struggled to detect very small increases in risk.

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