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Ambient Air Pollution and Traffic Exposures and Congenital Heart Defects in the San Joaquin Valley of California

Amy M. Padula[1], **Ira B. Tager**[2], **Suzan L. Carmichael**[1,2], **S. Katharine Hammond**[2], **Wei Yang**[1], **Frederick Lurmann**[3], and **Gary M. Shaw**[1]

[1]Stanford University 1265 Welsh Road Stanford, CA 94305

[2]University of California, Berkeley 1918 University Avenue, Suite 3C Berkeley, CA 94704

[3]Sonoma Technology Inc. 1455 North McDowell Boulevard Petaluma, CA 94954

Abstract

Background—Congenital anomalies are a leading cause of infant morbidity and mortality. Studies suggest associations between environmental contaminants and some anomalies, although evidence is limited.

Methods—We used data from the California Center of the National Birth Defects Prevention Study and the Children's Health and Air Pollution Study to estimate the odds of 27 congenital heart defects with respect to quartiles of 7 ambient air pollutant and traffic exposures in California during the first two months of pregnancy, 1997–2006 (N=813 cases and N=828 controls).

Results—Particulate matter <10 microns (PM_{10}) was associated with pulmonary valve stenosis ($aOR_{4th\ Quartile}$=2.6; 95% CI: 1.2, 5.7) and perimembranous ventricular septal defects ($aOR_{3rd\ Quartile}$=2.1; 95% CI: 1.1, 3.9) after adjusting for maternal race-ethnicity, education and multivitamin use. $PM_{2.5}$ was associated with transposition of the great arteries ($aOR_{3rd\ Quartile}$=2.6; 95% CI: 1.1, 6.5) and inversely associated with perimembranous ventricular septal defects ($aOR_{4th\ Quartile}$=0.5; 95% CI: 0.2, 0.9). Secundum atrial septal defects were inversely associated with carbon monoxide ($aOR_{4th\ Quartile}$=0.4; 95% CI: 0.2, 0.8) and $PM_{2.5}$ ($aOR_{4th\ Quartile}$=0.5; 95% CI: 0.3, 0.8). Traffic density was associated with muscular ventricular septal defects ($aOR_{4th\ Quartile}$=3.0, 95% CI: 1.2, 7.8) and perimembranous ventricular septal defects ($aOR_{3rd\ Quartile}$ =2.4; 95% CI: 1.3, 4.6), and inversely associated with transposition of the great arteries ($aOR_{4th\ Quartile}$=0.3; 95% CI: 0.1, 0.8).

Conclusions—PM_{10} and traffic density may contribute to the occurrence of pulmonary valve stenosis and ventricular septal defects, respectively. The results were mixed for other pollutants and had little consistency with previous studies.

There are a large number of epidemiologic studies of associations between ambient air pollution exposure during pregnancy and adverse birth outcomes, including low birth weight, preterm birth and infant mortality.(1–3) In contrast, evidence examining air pollution exposures in relation to congenital anomalies is more limited. Congenital

Corresponding Author: Amy M. Padula Stanford University 1265 Welsh Road Stanford, CA 94305 Ph: 650-724-1322 ampadula@stanford.edu.

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.(4) Congenital heart defects are the leading cause of infant deaths due to congenital anomalies.(5–7) The etiologies are unknown for the majority of these defects.

Associations with carbon monoxide exposure have been suggested for selected congenital heart defects(8–10) though carbon monoxide may be acting as a surrogate for another causal agent such as traffic exposure. A recent meta-analysis of air pollution and 7,663 heart defects found associations between nitrogen dioxide, particulate matter <10 microns and sulfur dioxide with coarctation of the aorta, tetralogy of Fallot and atrial septal defects.(11) However, in general the results of previous studies have not been consistent in terms of the specific pollutants, the congenital heart defect affected subgroups, nor the direction or strength of associations,(11) possibly due to the heterogeneity of the origin of these defects. These associations with congenital heart defects are anatomically, clinically, and epidemiologically heterogeneous(12) and; therefore, should be analyzed in designated phenotypic groupings rather than as a single overall group.(12)To address the need for more data on possible associations between specific phenotypes of congenital heart defects and air pollution exposure, we used data from the California Center of the National Birth Defects Prevention Study(14) and the Children's Health and Air Pollution Study to investigate whether ambient air pollution and metrics of traffic exposure contributed to the risks of congenital heart defects 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. Previous results have been described regarding the association between air pollution and other structural birth defects including neural tube defects, orofacial clefts and gastroshisis in this study population.(15)

Methods

Study population

The California Center of the National Birth Defects Prevention Study (NBDPS) is a collaborative partnership between Stanford University and the California Birth Defects Monitoring Program in the Department of Public Health. The Center has been collecting data from women residing in eight counties (San Joaquin, Stanislaus, Merced, Madera, Fresno, Kings, Tulare, and Kern) in the San Joaquin Valley since 1997.

Data were collected using active ascertainment by the California Birth Defects Monitoring Program. Case information was obtained from hospital reports and medical records and entered into a standardized database for clinician review and classification. Cases in the current analysis included infants with 27 heart defect groupings following the classification proposed by Botto et al.(12) All cases were confirmed by clinical, surgical, or autopsy reports. Cases resulting from known single gene or chromosomal abnormalities or with identifiable syndromes were ineligible for the study, given their presumed distinct underlying etiology. The majority (~74%) of cases was isolated; *i.e*., no additional major unrelated congenital anomaly.

Eligible cases included live births, stillbirths, and pregnancy terminations and were selected from the center's surveillance system based on strict eligibility criteria.(16) Controls included non-malformed live-born infants randomly selected from birth hospitals to represent the population from which the cases arose (approximately 150 per study year). Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, between six weeks and 24 months after the infant's estimated date of delivery. Estimated date of conception was derived by subtracting 266 days from expected date of delivery. Expected date of delivery was based on self-report; if unknown, it was estimated from information in the medical record (<2% of participants).

Interviews were conducted with mothers of 70% of eligible cases and 69% of controls. Mothers reported a full residential history from one month before conception through delivery, including start and stop dates for each residence. Mothers with diabetes (Type 1 or 2) prior to gestation were excluded (n=48). Addresses were geocoded using the Centrus Software (http://www.qmsoft.com/), which combines reference street networks from Tele Atlas (http://www.teleatlas.com/OurProducts/MapData/Dynamap/index.htm) and United States Postal Service data. Geocodes were available for 95% of cases and 93% of controls. The present analysis included 822 cases and 849 controls with an estimated delivery date between October 1, 1997 and December 31, 2006.

Exposure assessment

As part of the Children's Health and Air Pollution Study-San Joaquin Valley (CHAPSSJV), ambient air pollution measurements and traffic metrics were assigned to each of the geocoded residences reported by the study subjects during the first and second month of pregnancy. If there was more than one address during the period, the 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 accounted for at least 75% of the first and second month of pregnancy. Daily 24-hour averages of the pollutants: carbon monoxide (CO), nitrogen oxide (NO), nitrogen dioxide (NO_2), particulate matter less than 10 μm (PM_{10}), and PM less than 2.5 μm ($PM_{2.5}$) and a daily daytime 8-hour maximum of ozone were then averaged over the first two months of pregnancy.

The principal repository for U.S. ambient air quality data is the U.S. Environmental Protection Agency's Air Quality System database (www.epa.gov/ttn/airs/airsaqs). The station-specific daily air quality data were spatially interpolated using inverse distance-squared weighting. The data from one to four air quality measurement stations were included in each interpolation. When a residence was located within 5 km of one or more monitoring stations with valid observations, the interpolation was based solely on the nearby monitoring stations. Due to the regional nature of O_3, NO_2, PM_{10}, and $PM_{2.5}$ concentrations, a maximum interpolation radius of 50 km was used. NO and CO were interpolated using a smaller maximum interpolation radius of 25 km since they are directly emitted pollutants with larger spatial gradients.

The data for gaseous pollutants were measured using Federal Reference Method (FRM) continuous monitors. Particulate matter data were primarily limited to those collected with FRM 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 the traffic counts within a 300m radius of the early pregnancy residence. They were calculated from distance-decayed annual average daily traffic volumes(17) surrounding the geo-coded maternal residences. Roadway link-based traffic volumes were derived from Tele-Atlas/Geographic Data Technology traffic count data in 2005 using methodologies similar to those used in other health effects studies.(17) The Geographic Data Technology traffic count data were scaled to represent year 2003 traffic levels based on county average vehicle-miles-traveled growth rates (California Department of Transportation, 2004). Density plots were generated within a geographic information system using a linear decay function that approximates the fall-off of ambient concentrations with increasing distance away from roadways (*i.e*., decays to background within a given distance). Traffic density represents distance-decayed annual average daily traffic volume in both directions from all roads within the circular buffer. Traffic density is computed as if the wind directions were uniformly distributed around the compass and is symmetric on both sides of each roadway. The values are computed using the density function using a kernel with a 300 m search radius and 5 m grid resolution. In early analyses, we considered a radius of 150 m, though the estimates were not considerably different and previous literature focused on the 300 m radius.

Statistical analysis

Analyses were conducted to examine the association between the pollutants and traffic metrics. Each pollutant was examined by quartile as determined by the distribution in the controls. Traffic density was categorized into four groups: one for zero values and tertiles for the remaining non-zero values. Several potential covariates were also examined in relation to the exposures and the outcomes: maternal race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, or other); education (less than high school, high school, more than high school); age (<20, 20–35, >35 years); parity (0, 1, >1); early pregnancy multi-vitamin use (one month prior to and/or first two months of pregnancy); active and/or passive smoking during one month before through two months after conception; period of delivery (1997–2000, 2001–2003, 2004–2006); and infant sex.

Multivariable logistic regression analyses were conducted to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CI) reflecting the association between ambient air pollutants and traffic density and specific heart defect groupings.(12) Further, classification by isolated, multiple, or complex was not possible owing to sample size considerations. Multivariable analyses were performed adjusting for maternal race/ethnicity, education and early prenatal vitamin use. These covariates were selected *a priori* and based on causal assumptions derived from subject matter knowledge.(18) We considered the additional covariates and chose not to include them because they were colinear with other covariates (*e.g*., maternal age, parity), lacked indication as a confounder (e.g., infant sex), or had weak associations with the outcome and strong associations with the exposure (*e.g*., year of birth, season of birth).(19, 20) Stratum-specific odds ratios were compared to assess the role of

cigarette smoking as a potential modifier. Additionally, season of birth in this region is essentially a surrogate for many air pollutants rather than a confounder.

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

Results

In the original 1675 geocoded residences during the first two months of pregnancy and within the boundaries of San Joaquin Valley counties, 99.8% were assigned a value for at least one exposure metric. The completeness for specific exposures was 76% for CO, 85% for NO, 98% for NO_2, 97% for PM_{10}, 98% for ozone and 91% for traffic density. Among infants born with dates of conception in 1999 or later, 97% were assigned an estimate for $PM_{2.5}$ exposure. Cases had slightly higher (3%) completeness of exposure assignments for CO and NO compared to controls, but otherwise there was no difference.

The majority of mothers were Hispanic and had at least a high school education (Table 1). A quarter of the population was exposed to active or passive smoke. Mothers of cases were less likely to take multi-vitamins in early pregnancy and more likely to be multiparous.

The correlations of CO with NO (r=0.81), NO_2 (r=0.73) and $PM_{2.5}$ (r=0.84) were high, which reflects the common source of motor vehicles (Table 2). Ozone was negatively correlated with the traffic-related pollutants and traffic density was not correlated with any of the pollutants, as expected, due to the location of monitors away from sources (such as traffic) designed to capture regional air pollution.

Table 3 displays the results from the multivariable logistic regression models of each exposure and each heart defect group with at least 3 cases in each quartile of exposure and among participants with complete covariate data for the final model (N=1641). The crude results were not notably different from those shown. Partial anomalous pulmonary venous return, type A and type B interruption of the aortic arch, truncus arteriosus, Ebstein's anomaly, other ventricular septal defect, levo- transposition of the great arteries and other heart defects were not included because there were less than 3 cases per stratum. Our comments highlight results with odds ratios where the 95% confidence intervals did not include 1.0.

There was an inverse association between CO and risk of heterotaxia (aOR=0.2; 95% CI: 0.1, 0.7) comparing the second to first quartile and secundum atrial septal defects (aOR=0.4; 95% CI: 0.2, 0.8) comparing the highest to lowest quartile. No change in risk of congenital heart defects were associated with NO, NO_2 or O_3.

The odds of pulmonary valve stenosis was increased in the highest compared to the lowest quartile of PM_{10} exposure (aOR=2.6; 95% CI: 1.2, 5.7) and the increase of response by quartile was monotonic. The third quartile of PM_{10} was associated with perimembranous ventricular septal defects (aOR=2.1; 95% CI: 1.1, 3.9). The second and fourth quartiles had odds ratios >1, compared to the first quartile, though they were not statistically significant.

An increased odds of d-transposition of the great arteries was associated with the 3rd quartile of $PM_{2.5}$ (aOR=2.6, 95% CI: 1.1, 6.5). Similarly, the second and fourth quartiles had increased odds compared to the referent, though not statistically significant. We observed inverse associations between $PM_{2.5}$ and perimembranous ventricular septal defects (aOR=0.5; 95% CI: 0.2, 0.9) and secundum atrial septal defects (aOR= 0.5; 95% CI: 0.3, 0.8), comparing the highest to lowest quartile.

We observed positive associations between traffic density and ventricular septal defects, both muscular and perimembranous. The aOR comparing the highest quartile to the lowest for the muscular ventricular septal defects was 3.0 (95% CI: 1.2, 7.8). The second and third quartiles of traffic density were associated with perimembranous ventricular septal defects (aOR=2.4; 95% CI: 1.3, 4.6). The fourth quartile had increased odds as well, though lacked precision owing to small sample size. Traffic density was associated with secundum atrial septal defects comparing the second quartile to the 1st (aOR=2.4; 95% CI: 1.4, 4.0). The association was attenuated in the third and fourth quartiles. A decreased odds of d-transposition of the great arteries was associated with the highest quartile of traffic density (aOR=0.3, 95% CI: 0.1, 0.8).

For defect groups with fewer than 3 cases in the referent group, we collapsed exposure designations by using a median cut-off for the individual pollutants and a cut-off of 33rd percentile of the non-zero values for traffic density. We found associations between pulmonary atresia and traffic density (aOR=3.9; 95% CI: 1.2, 12.2), and other atrial septal defects and PM_{10} (aOR=5.1; 95% CI: 1.5, 17.9) for above versus below the cut-off.

Observed patterns of associations did not differ substantially in the stratum-specific results among those exposed to active and passive smoke (data not shown). Given sample size considerations, the precision on such estimates was poor.

Comments

We explored the relation between 7 air pollution related exposure metrics and 27 congenital heart defect groups. There was sufficient sample size to estimate potential associations for 19 defect groups. Although most pollutant-defect group comparisons did not provide clear evidence for associations, some statistically stable associations were notable. PM_{10} was associated with an increased odds of pulmonary valve stenosis and perimembranous ventricular septal defect, and $PM_{2.5}$ with d-transposition of the great arteries. Traffic density was positively associated with perimembranous ventricular septal defects, muscular ventricular septal defects and secundum atrial septal defects. Inverse associations were observed of CO with heterotaxia and secundum atrial septal defects, $PM_{2.5}$ with perimembranous ventricular septal defects and secundum atrial septal defects, and traffic with d-transposition of the great arteries.

The inconsistencies of the current results are not easily explained given the physical expectations from exposure science. These mixed results do not provide a clear conclusion about the association between air pollution and congenital heart defects. It is possible that either a) there are no associations between air pollution and congenital heart defects; b) our

data were not sufficient to detect and associations; c) there are confounding factors that were not measured that could clarify this relationship. In most cases, the exposure response was not monotonic as may be hypothesized. If there are vulnerable windows for certain heart defects that are narrower than our exposure period, we may have misclassified exposure. As with all birth defect studies, we are not able to account for early fetal loss that may bias the estimated odds ratios.

Two important considerations in the study of air pollution and congenital heart defects include rigorous case classification into specific defect groupings and precise spatiotemporal air pollution exposure assessment. The current study benefited from the rigorous case classification as part of the NBDPS. Secondly, the exposure assignments of the current study were able to incorporate residential history in early pregnancy, when the heart is formed. In a previous study of heart defects with 327 participants, 19% of cases and 23% of controls moved at least once between conception and delivery.(21) Previous studies of air pollution and congenital heart defects have relied on measurement of exposure at the birth residence rather than the residence early in pregnancy, thereby potentially misclassifying exposure for approximately 20% of their study population.(8, 9, 22–25) In some studies the exposure assignment relied on cruder spatial surrogates than residence such as zip code or a similar area measure.(10, 25) One study included traffic and meteorology in its spatiotemporal modeling of exposure.(24) However, none of these studies had considered residential history from early pregnancy and, therefore, could be subject to up to 20% of misclassification of exposure. NO and CO are particularly vulnerable to this misclassification due to the larger spatial gradients. The misclassification is likely less than 20% given most women do not move very far on average.

This is the first study to our knowledge to examine traffic density and congenital heart defects. Traffic density, which has been associated with other adverse birth outcomes such as low birth weight and preterm birth,(26–30) was associated with increased odds of three heart defects. An advantage of the traffic density parameter is that it accounts for the combined influence of all roadways and activity (for which data exist) near each residence location; however, wind direction was uniformly distributed.

The current study had a similar result to a study that found an association between PM_{10} and atrial septal defects, though our estimate was based on few cases comparing the above versus below median levels.(9) A recent meta-analysis of air pollution exposure and congenital anomalies reported increased odds of coarctation of the aorta and tetralogy of Fallot associated with NO_2.(11) The current study shows estimates in the same direction across quartiles, though not statistically precise. Thus, our observations supplement the evidence reviewed by Vrijheid et al.(11)

There are also incongruities between the current study and previous studies. Two previous studies reported an association between ozone and pulmonary artery valve defects,(10, 25) and two reported an association between CO and ventricular septal defects.(8, 10) The current study did not find positive associations of CO or ozone with any heart defect grouping and found inverse associations of heterotaxia and secundum atrial septal defects. Pulmonary valve stenosis was associated with PM_{10} in our study, but CO in a previous study

in Europe.(8) The explanation for these discrepancies is unknown, but may be due to diverse exposure levels or mixtures, imprecision of estimates due to small sample size, measurement or misclassification error, or different case ascertainment and classification definitions.

For example, the discordant results of traffic density and $PM_{2.5}$ were not expected and suggest that either or both may be subject to measurement or misclassification error. The pollutants are measured by monitors at the regional level and by design are located away from sources including heavy traffic. Traffic density captures the number of cars within 300 meters in a given day; however, the traffic counts are not available on all streets nor on all days and are therefore estimated and prone to error. Particulate matter is a unique pollutant because it is measured based on its mass rather than its composition, which may be the critical factor in the etiology of birth defects. Although not common, measurement of the chemical composition of particulate matter is critical for health studies. Future analyses will pursue individual constituents such as polycyclic aromatic hydrocarbons, which may clarify these inconsistent results.

Our results contribute to a modest body of epidemiologic evidence regarding associations between air pollution exposure and congenital anomalies. The current study suggests that exposures to increased levels of PM_{10} and traffic density during the first two months of pregnancy may contribute to the occurrence of pulmonary valve stenosis and ventricular septal defects, respectively, in the San Joaquin Valley of California. Due to the inconsistencies within and across studies and the multiple comparisons which have been done by all studies, more research is necessary to elucidate the potential relations between air pollution and congenital heart defects.

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Table 1

Demographic characteristics as percent of subjects between 1997 and 2006 in 8 counties in the San Joaquin Valley of California (N=1671).

	Percent of Cases (n=822)	Percent of Controls (n=849)
Maternal education (years)		
<12	35	32
12	29	27
>12	36	40
Missing	<1	<1
Maternal race/ethnicity		
White	29	31
Foreign-born Hispanic	34	29
U.S.- born Hispanic	23	26
Other	13	14
Missing	<1	<1
Multi-vitamin Use[a]		
Yes	62	65
No	37	33
Missing	1	2
Smoking[b]		
None	76	75
Active only	6	8
Passive only	11	10
Active and passive	6	6
Missing	<1	<1
Maternal age (years)		
<25	40	46
25–34	50	44
≥35	11	10
Infant sex		
Male	58	52
Female	42	48
Missing	<1	0
Plurality		
Singletons	94	99
Multiples	6	1
Parity		
0	32	39
1	30	31
2+	37	32
Year of expected delivery date		
1997–2000	27	37

	Percent of Cases (n=822)	Percent of Controls (n=849)
2001–2003	36	33
2004–2006	37	31

[a] Any folate-containing multi-vitamin use during one month before through two months after conception

[b] Any smoking during one month before through two months after conception

Table 2

Pearson correlation coefficients of exposures[a] among controls.

	CO	NO	NO_2	PM_{10}	$PM_{2.5}$	O_3 8-hour maximum	300m Traffic Density
CO	1						
NO	0.81	1					
NO_2	0.73	0.74	1				
PM_{10}	0.40	0.22	0.51	1			
$PM_{2.5}$	0.84	0.75	0.62	0.54	1		
O_3 8-hour maximum	−0.57	−0.71	−0.35	0.17	−0.61	1	
300m Traffic Density	0.01 p=0.76	0.03 p=0.40	0.11	−0.01 p=0.86	−0.004 p=0.92	0.02 p=0.61	1

p<0.05 except where noted

[a] Pollutant levels are based on 24-hour average measurements (except where noted)

Table 3

Adjusted[a] odds ratios (aOR) and 95% confidence intervals (CI) of congenital heart defects and exposure to pollutants[b] and traffic density[c] for N cases (N=1641).

	Exposure levels[b]	Heterotaxia		d-Transposition of the great arteries		Tetralogy of Fallot		Double outlet right ventricle - other		Double outlet right ventricle - TGA	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	16	Reference	12	Reference	22	Reference	6	Reference	5	Reference
	0.40–0.52	4	0.2 (0.1,0.7)	9	0.8 (0.3,1.9)	17	0.8 (0.4,1.6)	3	0.5 (0.1,1.9)	2	NC
	0.53–0.71	14	0.8 (0.4,1.7)	16	1.4 (0.6,3.0)	21	1.0 (0.5,1.9)	2	NC	3	0.6 (0.1,2.5)
	0.72–1.37	14	0.8 (0.4,1.8)	12	0.9 (0.4,2.2)	19	0.9 (0.5,1.8)	2	NC	4	0.8 (0.2,3.2)
NO (ppb)	0.69–4.14	15	Reference	12	Reference	23	Reference	4	Reference	2	--
	4.15–8.15	12	0.7 (0.3,1.6)	12	1.0 (0.5,2.4)	20	0.8 (0.4,1.6)	4	1.0 (0.2,4.0)	2	NC
	8.16–20.19	14	0.8 (0.4,1.8)	20	1.6 (0.7,3.4)	27	1.1 (0.6,2.1)	3	0.6 (0.1,2.9)	6	NC
	20.20–67.34	13	0.8 (0.4,1.7)	10	0.8 (0.4,2.0)	18	0.8 (0.4,1.5)	3	0.7 (0.1,3.2)	4	NC
NO_2 (ppb)	2.40–13.36	13	Reference	10	Reference	18	Reference	3	Reference	4	Reference
	13.37–16.81	20	1.4 (0.7,3.0)	16	1.6 (0.7,3.6)	34	1.8 (1.0,3.4)	1	NC	3	0.7 (0.2,3.3)
	16.82–20.53	14	1.0 (0.5,2.3)	16	1.6 (0.7,3.6)	26	1.4 (0.7,2.7)	7	2.2 (0.6,8.9)	3	0.7 (0.2,3.2)
	20.54–38.94	14	1.0 (0.5,2.2)	21	2.0 (0.9,4.4)	22	1.2 (0.6,2.4)	4	1.3 (0.3,5.8)	7	1.7 (0.5,6.1)
PM_{10} (μg/m^3)	7.90–25.24	17	Reference	12	Reference	26	Reference	2	---	5	Reference
	25.25–33.43	11	0.6 (0.3,1.3)	18	1.5 (0.7,3.1)	17	0.6 (0.3,1.2)	3	NC	3	0.6 (0.1,2.5)
	33.44–44.08	18	1.0 (0.5,2.0)	11	0.9 (0.4,2.0)	32	1.2 (0.7,2.1)	5	NC	1	NC
	44.09–95.32	17	0.9 (0.4,1.8)	22	1.9 (0.9,3.9)	24	0.9 (0.5,1.6)	6	NC	8	1.6 (0.5,5.0)
$PM_{2.5}$ (μg/m^3)	3.57–10.93	8	Reference	7	Reference	14	Reference	2	---	3	Reference
	10.94–14.82	16	1.8 (0.8,4.5)	15	2.2 (0.9,5.7)	22	1.6 (0.8,3.2)	6	NC	3	1.0 (0.2,5.1)
	14.83–26.12	15	1.8 (0.7,4.5)	18	2.6 (1.1,6.5)	23	1.6 (0.8,3.2)	2	NC	5	1.6 (0.4,7.0)
	26.13–66.29	12	1.4 (0.6,3.6)	10	1.5 (0.5,4.0)	22	1.5 (0.7,3.1)		NC	6	1.9 (0.5,8.0)
O_3 8-hour maximum (ppb)	10.49–29.05	16	Reference	12	Reference	25	Reference	2	---	4	Reference
	29.06–46.94	19	1.2 (0.6,2.4)	21	1.7 (0.8,3.6)	25	1.0 (0.6,1.8)	3	NC	6	1.5 (0.4,5.4)
	46.95–62.64	10	0.6 (0.3,1.4)	17	1.4 (0.6,3.0)	25	1.0 (0.6,1.9)	2	NC	6	1.6 (0.4,5.7)
	62.65–91.92	18	1.1 (0.5,2.3)	13	1.2 (0.5,2.7)	25	1.0 (0.6,1.8)	8	NC	1	NC

	Exposure levels[b]	Heterotaxia		d-Transposition of the great arteries		Tetralogy of Fallot		Double outlet right ventricle - other		Double outlet right ventricle - TGA	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
Traffic density[c]	0	18	Reference	27	Reference	28	Reference	4	Reference	4	Reference
	1–5031	13	1.0 (0.5,2.2)	9	0.6 (0.3,1.3)	24	1.3 (0.7,2.3)	4	1.6 (0.4,6.5)	2	NC
	5032–16717	19	1.4 (0.7,2.9)	19	1.2 (0.6,2.2)	22	1.1 (0.6,2.0)	4	1.6 (0.4,6.5)	3	1.2 (0.3,5.5)
	16718–135991	8	0.6 (0.2,1.4)	4	0.3 (0.1,0.8)	21	1.1 (0.6,2.0)	2	NC	5	2.0 (0.5,7.6)

	Exposure levels[b]	Atrioventricular septal defects		Total anomalous pulmonary venous return		Hypoplastic left heart syndrome		Coarctation of the aorta		Aortic stenosis	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	4	Reference	5	Reference	13	Reference	13	Reference	6	Reference
	0.40–0.52	3	0.7 (0.2,3.4)	4	0.8 (0.2,3.3)	11	0.8 (0.4,1.9)	15	1.1 (0.5,2.5)	2	NC
	0.53–0.71	4	0.9 (0.2,3.9)	2	NC	13	1.0 (0.5,2.3)	16	1.2 (0.6,2.7)	10	1.6 (0.6,4.6)
	0.72–1.37	1	NC	3	0.6 (0.1,2.7)	11	0.7 (0.3,1.7)	12	0.9 (0.4,2.1)	2	NC
NO (ppb)	0.69–4.14	3	Reference	7	Reference	12	Reference	15	Reference	4	Reference
	4.15–8.15	2	NC	4	0.6 (0.2,2.1)	13	1.2 (0.5,2.7)	20	1.3 (0.7,2.7)	5	1.3 (0.3,5.0)
	8.16–20.19	4	1.1 (0.2,5.3)	3	0.5 (0.1,1.8)	14	1.1 (0.5,2.6)	17	1.1 (0.5,2.4)	8	1.8 (0.5,6.2)
	20.20–67.34	4	1.2 (0.3,5.6)	5	0.7 (0.2,2.4)	14	1.2 (0.5,2.6)	18	1.2 (0.6,2.5)	6	1.4 (0.4,5.2)
NO_2 (ppb)	2.40–13.36	3	Reference	5	Reference	17	Reference	17	Reference	7	Reference
	13.37–16.81	4	1.2 (0.3,5.6)	10	2.1 (0.7,6.3)	17	1.0 (0.5,2.1)	18	1.1 (0.5,2.1)	7	1.0 (0.3,2.8)
	16.82–20.53	4	1.1 (0.2,5.1)	2	NC	14	0.9 (0.4,1.9)	22	1.3 (0.7,2.6)	7	0.9 (0.3,2.6)
	20.54–38.94	3	1.0 (0.2,4.9)	5	1.1 (0.3,3.7)	13	0.7 (0.3,1.6)	21	1.3 (0.6,2.5)	5	0.6 (0.2,2.0)
PM_{10} ($\mu g/m^3$)	7.90–25.24	2	--	6	Reference	15	Reference	16	Reference	7	Reference
	25.25–33.43	6	NC	8	1.3 (0.4,3.8)	22	1.5 (0.7,2.9)	14	0.8 (0.4,1.8)	6	0.8 (0.3,2.4)
	33.44–44.08	5	NC	6	1.0 (0.3,3.2)	12	0.8 (0.4,1.8)	22	1.4 (0.7,2.7)	9	1.1 (0.4,2.9)
	44.09–95.32	1	NC	4	0.7 (0.2,2.5)	11	0.7 (0.3,1.7)	23	1.4 (0.7,2.8)	4	0.5 (0.1,1.8)
$PM_{2.5}$ ($\mu g/m^3$)	3.57–10.93	4	Reference	4	Reference	14	Reference	13	Reference	3	Reference
	10.94–14.82	2	NC	4	1.0 (0.3,4.2)	10	0.8 (0.3,1.8)	16	1.2 (0.6,2.7)	9	3.1 (0.8,12.0)
	14.83–26.12	3	0.7 (0.1,3.1)	9	2.2 (0.7,7.4)	21	1.6 (0.8,3.3)	14	1.0 (0.5,2.2)	7	2.1 (0.5,8.4)
	26.13–66.29	4	0.8 (0.2,3.6)	4	1.0 (0.3,4.2)	12	0.9 (0.4,2.0)	16	1.2 (0.6,2.6)	4	1.2 (0.3,5.4)
O_3 8-hour maximum (ppb)	10.49–29.05	5	Reference	3	Reference	19	Reference	17	Reference	6	Reference

	Exposure levels[b]	Atrioventricular septal defects		Total anomalous pulmonary venous return		Hypoplastic left heart syndrome		Coarctation of the aorta		Aortic stenosis	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
	29.06–46.94	4	0.9 (0.2,3.3)	8	2.6 (0.7,10.1)	16	0.8 (0.4,1.6)	22	1.3 (0.7,2.5)	9	1.6 (0.5,4.6)
	46.95–62.64	2	NC	7	2.4 (0.6,9.5)	13	0.6 (0.3,1.3)	15	0.9 (0.4,1.9)	8	1.5 (0.5,4.4)
	62.65–91.92	3	0.6 (0.1,2.6)	5	1.7 (0.4,7.0)	13	0.7 (0.3,1.5)	23	1.4 (0.7,2.6)	3	0.6 (0.1,2.4)
Traffic density[c]	0	8	---	6	Reference	14	Reference	22	Reference	10	Reference
	1–5031	1	NC	3	0.7 (0.2,2.9)	14	1.5 (0.7,3.3)	19	1.3 (0.7,2.4)	5	0.9 (0.3,2.7)
	5032–16717	2	NC	9	2.1 (0.7,6.0)	15	1.6 (0.7,3.4)	18	1.2 (0.6,2.4)	4	0.7 (0.2,2.3)
	16718–135991	2	NC	3	0.7 (0.2,2.9)	13	1.6 (0.7,3.5)	13	0.9 (0.4,1.8)	5	0.9 (0.3,2.8)

	Exposure levels[b]	Pulmonary atresia		Tricuspid atresia		Pulmonary valve stenosis		Ventricular septal defects - perimembranous		Ventricular septal defects - muscular	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	4	Reference	5	Reference	14	Reference	28	Reference	16	Reference
	0.40–0.52	6	1.5 (0.4,5.4)	4	0.9 (0.2,3.4)	13	0.9 (0.4,2.1)	19	0.7 (0.4,1.3)	9	0.6 (0.3,1.5)
	0.53–0.71	1	NC	1	NC	11	0.8 (0.3,1.7)	18	0.6 (0.3,1.2)	10	0.6 (0.3,1.5)
	0.72–1.37	7	1.7 (0.5,6.0)	2	NC	8	0.6 (0.2,1.4)	15	0.5 (0.3,1.0)	6	0.4 (0.2,1.1)
NO (ppb)	0.69–4.14	2	---	5	Reference	14	Reference	23	Reference	15	Reference
	4.15–8.15	6	NC	4	0.8 (0.2,3.2)	11	0.8 (0.3,1.8)	19	0.8 (0.4,1.5)	8	0.6 (0.2,1.3)
	8.16–20.19	4	NC	5	1.0 (0.3,3.6)	12	0.8 (0.4,1.9)	22	0.9 (0.5,1.7)	13	0.9 (0.4,2.0)
	20.20–67.34	6	NC	2	NC	13	0.9 (0.4,2.0)	24	1.0 (0.5,1.8)	10	0.7 (0.3,1.6)
NO_2 (ppb)	2.40–13.36	2	---	5	Reference	15	Reference	25	Reference	14	Reference
	13.37–16.81	6	NC	6	1.2 (0.4,4.0)	18	1.2 (0.6,2.4)	32	1.2 (0.7,2.2)	16	1.2 (0.5,2.5)
	16.82–20.53	6	NC	4	0.8 (0.2,3.0)	12	0.8 (0.4,1.8)	22	0.8 (0.5,1.6)	7	0.5 (0.2,1.3)
	20.54–38.94	5	NC	3	0.6 (0.1,2.5)	14	0.9 (0.4,2.0)	19	0.7 (0.4,1.4)	11	0.8 (0.4,1.9)
PM_{10} (μg/m^3)	7.90–25.24	2	---	3	Reference	9	Reference	15	Reference	11	Reference
	25.25–33.43	5	NC	4	1.3 (0.3,5.8)	13	1.4 (0.6,3.5)	28	1.8 (0.9,3.5)	9	0.8 (0.3,2.0)
	33.44–44.08	6	NC	9	3.0 (0.8,11.2)	15	1.7 (0.7,3.9)	32	2.1 (1.1,3.9)	15	1.4 (0.6,3.1)
	44.09–95.32	6	NC	2	NC	23	2.6 (1.2,5.7)	21	1.3 (0.7,2.7)	13	1.2 (0.5,2.7)
$PM_{2.5}$ (μg/m^3)	3.57–10.93	5	Reference	4	Reference	10	Reference	28	Reference	15	Reference
	10.94–14.82	3	0.6 (0.1,2.4)	4	0.9 (0.2,3.8)	17	1.7 (0.8,3.9)	20	0.7 (0.4,1.3)	8	0.5 (0.2,1.3)
	14.83–26.12	3	0.6 (0.1,2.4)	1	NC	23	2.2 (1.0,4.9)	27	0.9 (0.5,1.6)	11	0.7 (0.3,1.5)
	26.13–66.29	5	0.9 (0.3,3.3)	5	1.2 (0.3,4.7)	9	0.9 (0.3,2.2)	14	0.5 (0.2,0.9)	10	0.6 (0.3,1.5)

	Exposure levels[b]	Pulmonary atresia		Tricuspid atresia		Pulmonary valve stenosis		Ventricular septal defects - perimembranous		Ventricular septal defects - muscular	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
O_3 8-hour maximum (ppb)	10.49–29.05	4	Reference	4	Reference	12	Reference	24	Reference	9	Reference
	29.06–46.94	6	1.5 (0.4,5.6)	5	1.3 (0.3,4.9)	9	0.7 (0.3,1.8)	26	1.1 (0.6,2.0)	7	0.8 (0.3,2.2)
	46.95–62.64	4	1.0 (0.2,4.2)	4	1.0 (0.2,4.0)	18	1.5 (0.7,3.2)	23	1.0 (0.5,1.8)	18	2.1 (0.9,4.9)
	62.65–91.92	5	1.3 (0.3,4.9)	5	1.2 (0.3,4.7)	20	1.7 (0.8,3.5)	25	1.1 (0.6,2.0)	14	1.6 (0.7,3.8)
Traffic density[c]	0	1	---	4	Reference	21	Reference	18	Reference	7	Reference
	1–5031	3	NC	3	1.1 (0.2,4.9)	12	0.8 (0.4,1.8)	28	2.4 (1.3,4.6)	15	3.4 (1.3,8.7)
	5032–16717	6	NC	5	1.6 (0.4,6.4)	11	0.8 (0.4,1.6)	29	2.4 (1.3,4.6)	8	1.7 (0.6,4.8)
	16718–135991	7	NC	4	1.3 (0.3,5.5)	13	0.9 (0.4,1.9)	18	1.5 (0.8,3.0)	14	3.0 (1.2,7.8)

	Exposure levels[b]	Ventricular septal defects - conov		Secundum atrial septal defects		Other atrial septal defects		Single ventricle or other complex	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
CO (ppm)	0.13–0.39	4	Reference	38	Reference	6	Reference	5	Reference
	0.40–0.52	4	1.0 (0.2,4.3)	29	0.8 (0.5,1.4)	5	0.8 (0.2,2.7)	4	0.8 (0.2,3.1)
	0.53–0.71	6	1.5 (0.4,5.5)	29	0.8 (0.5,1.4)	1	NC	5	1.0 (0.3,3.6)
	0.72–1.37	2	NC	15	0.4 (0.2,0.8)	2	NC	4	0.8 (0.2,3.1)
NO (ppb)	0.69–4.14	3	Reference	31	Reference	6	Reference	5	Reference
	4.15–8.15	7	2.2 (0.6,8.9)	24	0.8 (0.4,1.4)	5	0.7 (0.2,2.5)	7	1.4 (0.4,4.7)
	8.16–20.19	2	NC	36	1.2 (0.7,2.0)	1	NC	2	NC
	20.20–67.34	5	1.6 (0.4,6.8)	32	1.0 (0.6,1.8)	4	0.7 (0.2,2.4)	5	1.0 (0.3,3.6)
NO_2 (ppb)	2.40–13.36	5	Reference	35	Reference	3	Reference	7	Reference
	13.37–16.81	3	0.6 (0.1,2.5)	48	1.4 (0.9,2.2)	9	3.0 (0.8,11.4)	4	0.6 (0.2,2.1)
	16.82–20.53	6	1.2 (0.3,3.9)	29	0.8 (0.5,1.4)	4	1.3 (0.3,5.9)	6	1.0 (0.3,2.9)
	20.54–38.94	5	1.0 (0.3,3.5)	28	0.8 (0.5,1.4)	2	NC	4	0.6 (0.2,2.0)
PM_{10} (μg/m^3)	7.90–25.24	2	---	34	Reference	1	---	7	Reference
	25.25–33.43	6	NC	41	1.2 (0.7,1.9)	2	NC	4	0.6 (0.2,1.9)
	33.44–44.08	4	NC	34	1.0 (0.6,1.7)	8	NC	3	0.5 (0.1,1.8)
	44.09–95.32	7	NC	30	0.9 (0.5,1.5)	7	NC	7	1.0 (0.3,3.0)
$PM_{2.5}$ (μg/m^3)	3.57–10.93	5	Reference	45	Reference	5	Reference	4	Reference
	10.94–14.82	5	1.0 (0.3,3.5)	20	0.5 (0.3,0.8)	3	0.6 (0.1,2.7)	8	2.0 (0.6,6.9)

	Exposure levels[b]	Ventricular septal defects - conov		Secundum atrial septal defects		Other atrial septal defects		Single ventricle or other complex	
		N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)	N	AOR (95% CI)
O_3 8-hour maximum (ppb)	14.83–26.12	6	1.2 (0.4,4.1)	42	0.9 (0.6,1.5)	5	0.9 (0.3,3.3)	3	0.7 (0.2,3.2)
	26.13–66.29	1	NC	21	0.5 (0.3,0.8)	3	0.6 (0.1,2.6)	4	1.0 (0.2,4.0)
	10.49–29.05	2	---	39	Reference	3	Reference	5	Reference
	29.06–46.94	5	NC	31	0.8 (0.5,1.4)	4	1.4 (0.3,6.2)	6	1.2 (0.4,4.1)
	46.95–62.64	8	NC	39	1.0 (0.6,1.6)	2	NC	5	1.0 (0.3,3.6)
	62.65–91.92	4	NC	31	0.8 (0.5,1.4)	9	3.1 (0.8,11.7)	5	1.0 (0.3,3.5)
Traffic density[c]	0	9	Reference	28	Reference	4	Reference	7	Reference
	1–5031	3	0.5 (0.1,1.8)	44	2.4 (1.4,4.0)	6	2.7 (0.7,9.7)	8	1.6 (0.6,4.6)
	5032–16717	5	0.7 (0.2,2.1)	28	1.4 (0.8,2.5)	3	1.3 (0.3,6.0)	4	0.8 (0.2,2.9)
	16718–135991	2	NC	27	1.4 (0.8,2.5)	4	1.7 (0.4,6.9)	3	0.6 (0.2,2.5)

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

NC = not calculated

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

[b] Pollutant levels are based on 24-hour average measurements (except ozone, which is a daytime 8-hour maximum), and then averaged over 1st and 2nd 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-zero values

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