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Association between First Trimester Exposure to Ambient $PM_{2.5}$ and NO_2 and Congenital Heart Defects: A Population-Based Cohort Study of 1,342,198 Live Births in Canada

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Background: The extent to which ambient air pollution contributes to the pathogenesis of congenital heart defects remains uncertain.

Objective: We investigated whether first trimester exposure to ambient fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) was associated with the risk of critical and noncritical heart defects in a large population-based cohort of births.

Methods: We carried out a retrospective cohort study of children conceived between 2000 and 2016 in Quebec, Canada. Heart defects were identified via data from the Maintenance and Use of Data for the Study of Hospital Clientele registry. The main exposures were average concentration of $PM_{2.5}$ and NO_2 in *a*) the first trimester and *b*) the month of conception. Exposures were estimated at the residential postal code. Associations with critical and noncritical heart defects were assessed using logistic regression models, adjusted for maternal and infant characteristics. We considered single- and two-pollutant models and assessed modifying effects of maternal comorbidity, including preexisting hypertension, preeclampsia, anemia, and diabetes.

Results: The cohort comprised 1,342,198 newborns, including 12,715 with heart defects. Exposure in the first trimester and month of conception yielded similar results; both were associated with a greater risk of heart defects. Adjusted odds ratios (OR) for any heart defect per interquartile range increase were 1.02 (95% CI: 1.00, 1.05) for $PM_{2.5}$ and 1.10 (95% CI: 1.07, 1.13) for NO_2. Associations with atrial septal defects were 1.08 (95% CI: 1.03, 1.14) for $PM_{2.5}$ and 1.19 (95% CI: 1.12, 1.25) for NO_2. Corresponding ORs for ventricular septal defects and individual critical heart defects were not significant. $PM_{2.5}$ (OR = 1.11; 95% CI: 1.06, 1.17) and NO_2 (OR = 1.23; 95% CI: 1.17, 1.31) exposure were associated with a greater risk of heart defects in mothers with comorbidity.

Discussion: In this population-based cohort, prenatal exposure to ambient air pollution during the first trimester was associated with an increased risk of heart defects, particularly atrial septal defects. The association with heart defects was greater in mothers with comorbidity. https://doi.org/10.1289/EHP11120

Introduction

Congenital heart anomalies are prevalent and account for nearly one-third of birth defects.[1] In North America, 1.5% of newborns have heart defects.[2] Heart defects are a leading cause of disability and infant mortality, but their etiology is poorly understood.[3] Although it is established that genes are involved in many congenital anomalies, the contribution of modifiable risk factors is unclear.[4,5] Approximately 50% of heart defects cannot be linked to a specific cause, and the proportion of potentially preventable cases could be as high as 30%.[5]

Environmental exposures are thought to play a role in the development of congenital heart anomalies. Several studies have reported associations between air pollutants and the risk of heart defects, including atrial septal defects, coarctation of the aorta, and tetralogy of Fallot.[6–15] However, lack of statistical power and problems with exposure assessment have been major limitations of this work.[16–18] In most studies, exposures are assigned using monitoring stations nearest to the residence or include only subjects within a fixed radius. These methods of assessing exposure do not account for spatial variation of pollutants, which may lead to considerable exposure misclassification. In this study, we assessed whether spatiotemporal concentrations of fine particulate matter ($PM_{2.5} < 2.5$ μm in aerodynamic diameter) and nitrogen dioxide (NO_2) were associated with the risk of critical and noncritical heart defects in a large population-based cohort of births in Canada.

Materials and Methods

Study Design and Population

We performed a retrospective cohort study of all hospital deliveries in the province of Quebec, Canada, using health administrative data. We restricted the cohort to newborns conceived between 2000 and 2016, the period when pollution data were collected. The cohort captures most of the population given that 98% of newborns in Quebec are delivered in hospital. Data were obtained from the Maintenance and Use of Data for the Study of Hospital Clientele registry, which contains discharge summaries with diagnostic information for all hospitalizations in Quebec. The data are coded by trained hospital archivists and validated through rigorous algorithms.[19] Maternal chart numbers were recorded on newborn discharge summaries, which allowed us to link mothers with their infants. We excluded stillbirths because information on heart defects was not available. Given that the data were anonymized and the study conformed to the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*,[20] our research institution issued a waiver from ethical review.

Congenital Heart Defects

The primary outcome included heart defects documented at delivery. Heart defects were identified during ultrasound screening in the second or third trimester or during clinical examination upon delivery. Heart defects were documented on physician discharge

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summaries and coded using diagnostic codes in the 9th and 10th revisions of the *International Classification of Diseases* (ICD-9[21] and ICD-10[22]), and procedure codes in the *Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures*[23] and *Canadian Classification of Health Interventions*[24] (Table 1).

We classified heart defects as critical (tetralogy of Fallot, coarctation of the aorta, transposition of great vessels, truncus arteriosus, hypoplastic left heart, common ventricle, other) or noncritical (atrial septal defect, ventricular septal defect, endocardial cushion defect, pulmonary artery defects, heterotaxy, other).[25] Critical defects require urgent intervention at birth and may cause severe sequalae or death if not treated promptly.[26]

We further evaluated four specific types of defects that were the focus of prior studies on heart defects and air pollution exposure: tetralogy of Fallot, coarctation of the aorta, atrial septal defects, and ventricular septal defects.[16] Anomalies were not mutually exclusive. Because the atrium may not fully develop before 37 wk of gestation, we restricted the analysis of atrial septal defects to term births only.[27]

Air Pollution Exposure

Organogenesis in humans occurs in the first trimester of pregnancy, with different organ systems having varying periods of susceptibility to teratogenic agents. Except for the atrial septum, the fetal heart is fully formed by the 10th week of gestation.[27] We therefore considered the first trimester of pregnancy as the critical window of exposure. We estimated the start and end date of the first trimester for each fetus. To calculate the date of conception, we subtracted the gestational age from the date of birth, and added 2 wk to account for the timing of ovulation after the last menstrual period. The date of birth and gestational age in completed weeks were documented on the infant chart. Gestational age was determined by dating ultrasounds in the first trimester.

The exposures of interest were ambient $PM_{2.5}$ and NO_2, two principal ambient air pollutants. We considered two exposure metrics: *a*) average concentration of pollutants in the month of conception and *b*) average exposure in the first trimester defined as the month of conception and the two following months. These exposures were assessed using spatially resolved monthly mean concentrations of ambient $PM_{2.5}$ and NO_2 extracted from the Canadian Urban Environmental Health Research Consortium.[28–30] Exposures were assigned to newborns using the mother's six-digit residential postal code and date of conception. Exposure data were measured at the postal code, a fine geographic level that covers one side of a street block in urban areas, although areas covered may be greater in rural settings.

Monthly $PM_{2.5}$ concentrations were estimated at a $0.01^\circ \times 0.01^\circ$ resolution (~ 1 km $\times$ 1 km) from satellite observations of aerosol optical depth based on the Moderate Resolution Imaging Spectroradiometer from the National Aeronautics and Space Administration Terra satellite.[29] Estimates were calibrated using an optimal estimation algorithm incorporating ground-based observations in conjunction with a geographically weighted regression of urban land cover, elevation, and aerosol composition.[29] The annual estimates from this model closely agree with long-term cross-validated ground measurements at fixed-site monitors across North America ($r^2 = 0.70$).[29]

Ambient NO_2 concentrations at residential postal codes were estimated from a national land-use regression model developed from fixed-site measurements at Environment Canada's National Air Pollution Surveillance (NAPS) system.[28,31] The model included satellite estimates of NO_2, road length, industrial land use, and summer rainfall, and incorporated a distance–decay gradient based on proximity to highways and major roads to account for fine-scale geographic variability of NO_2 from vehicle emissions. The model explained 73% of the variation in 2006 annual NAPS NO_2 measurements. Monthly estimates were produced using ratios of measured monthly data over the measured annual average from NAPS stations across Canada.

Statistical Analysis

We assessed the association between prenatal exposure to ambient $PM_{2.5}$ and NO_2 and the odds of congenital heart defects using multivariable logistic regression. A directed acyclic graph (DAG) outlining the conceptual relation between congenital heart defects and first trimester exposure to ambient $PM_{2.5}$ and NO_2 is provided in Figure S1. We treated the two main exposure metrics, including *a*) average concentration in the month of conception, and *b*) average concentration in the first trimester, as continuous variables and assessed Pearson correlation coefficients. We fitted single-pollutant models, as well as two-pollutant models accounting for coexposure to $PM_{2.5}$ and NO_2.

Models were adjusted for the following covariates to be consistent with previous studies[7,14,32,33]: sex, birth year, maternal age (continuous), parity (zero, one, or two or more), multiple

Table 1. International Classification of Disease (ICD) codes for heart defect.

	ICD-9 codes[a]	ICD-10 codes[a]
Critical heart defect		
Tetralogy of Fallot	745.2 (47.81)	Q21.3 (1.HP.87, 1.LD.84)
Transposition of great vessels	745.1	Q20.1–Q20.3, Q20.50
Truncus arteriosus	745.0 (47.83)	Q20.0, Q21.4 (1.LA.84)
Hypoplastic left heart	746.7	Q23.4
Common ventricle	745.3	Q20.4
Coarctation of aorta	747.1	Q25.1
Other critical	746.01, 746.1, 746.2, 747.41	Q22.0, Q22.4, Q22.5, Q26.2
Noncritical heart defect		
Endocardial cushion	745.6 (47.55, 47.64, 47.74)	Q21.2 (1.LC.84)
Ventricular septum	745.4 (47.54, 47.63, 47.73)	Q21.0, Q21.8 (1.HR.80)
Atrial septum	745.5 (47.52, 47.53, 47.62, 47.72)	Q21.1 (1.HN.80)
Valve	746.00, 746.02, 746.09, 746.3–746.6	Q22.1–Q22.3, Q22.8–Q23.3, Q23.8, Q23.9
Aorta	747.2	Q25.2–Q25.4
Pulmonary artery	747.3	Q25.5–Q25.7
Heterotaxy	746.87, 759.3	Q20.58, Q20.6, Q24.0, Q24.1, Q89.3
Other	Any defects in 745–746, 747.1–747.4 not listed above	Any defects in Q20–Q24.9, Q25.1–Q26.4, Q26.8, Q26.9 not listed above

Note: ICD-9, *International Classification of Diseases, Ninth Revision*[21]; ICD-10, *International Classification of Diseases, Tenth Revision*.[22]
[a]Values in parentheses refer to procedure codes (*Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures*[23]; *Canadian Classification of Health Interventions*[24]).

birth (yes/no), season of conception (fall, winter, spring, summer), rural or urban residence, and neighborhood material deprivation quintile (an index based on census data for average personal income, employment rate, and population without a high school diploma[34]). Although not all these variables are confounders in the typical sense, we adjusted for them nevertheless given that they may reduce bias from conditioning on live birth, as illustrated in the DAG (Figure S1).[35,36] For the same reason, we adjusted the models for maternal comorbidity (treated as one variable; yes/no), including anemia, obesity, preeclampsia, preexisting hypertension, preexisting diabetes types 1 or 2, epilepsy or mood disorders, and substance use disorders (tobacco, alcohol, illicit drugs). These morbidities may be involved in pregnancy loss and are associated with a greater risk of heart defects.[37,38] We obtained data for all these morbidities from the Maintenance and Use of Data for the Study of Hospital Clientele registry. We did not include gestational diabetes as a comorbidity because the onset of hyperglycemia is usually in the second trimester after the fetal heart has formed.

For all continuous variables (i.e., each pollutant and maternal age), we assessed nonlinearity of the relationship with heart defects using natural cubic splines with 3 degrees of freedom. We examined spline plots and compared the fit of linear and spline models using the Akaike information criterion.

In sensitivity analysis, we excluded newborns with multiple congenital anomalies. Because some studies suggest that air pollutants may have a greater effect on birth outcomes in women with preexisting morbidity,[39,40] we carried out subgroup analyses to assess modifying effects of different the comorbidities listed above. We used Cochran's Q test to assess heterogeneity across subgroups.[41] We also assessed modifying effects of season of conception, given that hot temperature[42–44] and infection (respiratory/influenza)[45] may influence the risk of heart defects. We performed subgroup analyses according to urban and rural residence because pollution mixtures in urban areas may differ. For the same reason, we assessed whether associations varied when we restricted the data to Montreal, the most populated region in Quebec. All statistical analyses were performed using R software (version 4.1.1; R Development Core Team).

Results

The cohort included 1,342,198 newborns conceived between 2000 and 2016 (Table 2). A total of 12,715 newborns were diagnosed with heart defects, for a prevalence of 9.5 cases [95% confidence interval (CI): 9.3, 9.6] per 1,000 births. Of 12,715 newborns diagnosed with heart defects, 2,592 had multiple anomalies. Maternal age (>40 y), multiple birth, and comorbidity were associated with a higher prevalence of heart defects.

Average monthly exposures to pollutants in the first trimester were 8.0 $\mu g/m^3$ [interquartile range (IQR): 3.3 $\mu g/m^3$] for $PM_{2.5}$ and 11.3 ppb (IQR: 11.4 ppb) for NO_2 (Table 3). Exposures in the month of conception and first trimester were highly correlated ($r = 0.81$ for $PM_{2.5}$ and 0.97 for NO_2) (Table S1).

For both $PM_{2.5}$ and NO_2, we found no evidence of nonlinearity in the relationship with heart defects (Figure S2 and Table S3), but the association between maternal age and heart defects was nonlinear (Figure S3). Air pollutant exposure in the first trimester was associated with greater odds of heart defects (Table 4). In single-pollutant models, the estimated odds ratio (OR) for an increase of 1 IQR was 1.02 for $PM_{2.5}$ (95% CI: 1.00, 1.05) and 1.10 for NO_2 (95% CI: 1.07, 1.13). Exposures in the month of conception yielded similar results; adjusted ORs were 1.01 (95% CI: 0.99, 1.04) for $PM_{2.5}$ and 1.10 (95% CI: 1.07, 1.13) for NO_2. In two-pollutant models, the association between NO_2 and heart defects increased slightly (OR = 1.11; 95% CI: 1.08, 1.15), whereas the association for $PM_{2.5}$ was attenuated (OR = 0.98; 95% CI: 0.96, 1.00).

There were in total 1,400 critical and 12,053 noncritical heart defects (Table 5). Exposure to pollutants in the first trimester was associated with noncritical heart defects. Adjusted ORs for noncritical defects were 1.03 per IQR increment in $PM_{2.5}$ (95% CI: 1.00, 1.05) and 1.11 per IQR increment in NO_2 (95% CI: 1.08, 1.14). $PM_{2.5}$ (OR = 1.08; 95% CI: 1.03, 1.14) and NO_2 (OR = 1.19; 95% CI: 1.12, 1.25) were both associated with the risk of atrial septal defects. However, there was no association with ventricular septal defects. Associations appeared to be present with tetralogy of Fallot for $PM_{2.5}$ and with coarctation of the aorta for both pollutants, but CIs included the null owing to the small number of cases. Excluding newborns with multiple anomalies did not meaningfully influence associations for noncritical heart defects and

Table 2. Prevalence of any heart defects according to maternal and infant characteristics, Quebec (Canada), 2000–2016 (newborns, $N = 1,342,198$; defects, $N = 12,715$).

		Any heart defect	
	Newborns (*n*)	Defects (*n*)	Prevalence per 1,000 (95% CI)
Maternal age (y)			
<20	36,272	370	10.2 (9.2, 11.2)
20–29	651,009	5,861	9.0 (8.9, 9.2)
30–39	618,098	5,983	9.7 (9.4, 9.9)
≥40	36,819	501	13.6 (12.4, 14.8)
Comorbidity			
Any	180,454	3,013	16.7 (16.1, 17.3)
Obesity	28,095	417	14.8 (13.4, 16.3)
Diabetes type 1 or 2	11,161	429	38.4 (34.9, 42.0)
Preeclampsia, gestational hypertension	47,146	719	15.3 (14.1, 16.4)
Preexisting hypertension	20,936	340	17.6 (15.6, 19,6)
Epilepsy and mood disorders	7,076	119	16.8 (13.8, 19.8)
Anemia	70,969	1,476	15.3 (14.1, 16.4)
Substance use disorder	24,175	273	11.3 (10.0, 12.6)
Multiple comorbidities	21,104	569	27.0 (24.8, 29.1)
No comorbidity	1,161,744	9,702	8.4 (8.2, 8.5)
Multiple birth			
Yes	38,890	769	19.8 (18.4, 21.2)
No	1,303,308	11,946	9.2 (9.0, 9.3)
Parity			
0	668,966	6,435	9.6 (9.6, 9.9)
1	465,008	4,208	9.1 (9.1, 9.3)
≥2	208,224	2,072	10.0 (9.5, 10.4)
Infant sex	1,342,198	12,715	9.5 (9.3, 9.6)
Male	688,118	6,501	9.5 (9.2, 9.7)
Female	654,080	6,214	9.5 (9.3, 9.7)
Neighborhood deprivation			
Low	240,032	2,082	8.7 (8.5, 9.2)
Low-moderate	262,147	2,383	9.1 (8.3, 9.0)
Moderate	259,752	2,431	9.4 (9.0, 9.7)
Moderate-high	260,031	2,485	9.6 (9.2, 9.9)
High	271,773	2,863	10.5 (10.2, 10.9)
Unknown	48,463	471	9.7 (8.9, 10.6)
Residence			
Urban	1,076,888	10,249	9.5 (9.3, 9.7)
Montreal	359,423	3,840	10.7 (10.3, 11.0)
Rural	249,055	2,323	9.3 (9.0, 9.7)
Season of conception			
Winter	402,516	3,890	9.7 (9.1, 9.8)
Spring	384,725	3,714	9.7 (9.4, 10.1)
Summer	415,559	4,007	9.4 (9.1, 9.7)
Fall	417,892	3,972	9.3 (9.0, 9.6)
Time period			
2000–2009	701,193	6,954	9.9 (9.7, 10.1)
2010–2016	641,005	5,761	9.0 (8.8, 9.2)

Note: CI, confidence interval.

Table 3. Distribution of ambient $PM_{2.5}$ and NO_2 in the month of conception and first trimester of pregnancy among 1,342,198 newborns in Quebec (Canada), 2000–2016.

			Percentile of distribution					
	Mean	SD	5th	25th	50th	75th	95th	IQR
$PM_{2.5}$ ($\mu g/m^3$)								
First trimester	8.0	2.7	3.6	6.3	8.1	9.6	12.4	3.3
Month of conception	7.9	3.2	3.1	5.8	7.7	9.8	13.1	4.0
NO_2 (ppb)								
First trimester	11.3	8.6	2.3	4.6	8.74	16.0	28.8	11.4
Month of conception	11.3	8.8	2.2	4.6	8.6	15.8	29.3	11.2

Note: IQR, interquartile range, NO_2, nitrogen dioxide; $PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm; SD, standard deviation.

coarctation of the aorta, but tetralogy of Fallot no longer appeared associated with air pollution (Table S4).

Assessment of modifying effects of maternal comorbidity revealed significant heterogeneity (Table 6). $PM_{2.5}$ in the first trimester was associated with an OR of 1.11 for heart defects among mothers with any comorbidity (95% CI: 1.06, 1.17), but an OR of 0.99 among mothers without comorbidity (95% CI: 0.97, 1.02) (Cochran's Q $p < 0.001$). For NO_2, ORs were 1.23 for mothers with comorbidity (95% CI: 1.17, 1.31) and 1.06 for mothers without comorbidity (95% CI: 1.03, 1.09) (Cochran's Q $p < 0.001$). The association between air pollutants and heart defects was stronger among women with anemia [$OR_{PM2.5} = 1.21$ (95% CI: 1.13, 1.31); $OR_{NO2} = 1.28$ (95% CI: 1.18, 1.38)], epilepsy and mood disorders [$OR_{PM2.5} = 1.24$ (95% CI: 0.95, 1.62); $OR_{NO2} = 1.54$ (95% CI: 1.13, 2.10)], preexisting hypertension [$OR_{PM2.5} = 1.20$ (95% CI: 1.03, 1.41); $OR_{NO2} = 1.15$ (95% CI: 0.96, 1.36)], and preeclampsia [$OR_{PM2.5} = 1.07$ (95% CI: 0.95, 1.19); $OR_{NO2} = 1.21$ (95% CI: 1.08, 1.36)].

Additional subgroup analysis showed positive associations with any heart defect in Montreal [$OR_{PM2.5} = 1.03$ (95% CI: 0.98, 1.09); $OR_{NO2} = 1.13$ (95% CI: 1.06, 1.20)], but no association outside Montreal [$OR_{PM2.5} = 0.98$ (95% CI: 0.95, 1.01); $OR_{NO2} = 0.97$ (95% CI: 0.92, 1.02)] (Table S5). NO_2 was more strongly associated with heart defects among women who conceived in the spring.

Discussion

In this population-based cohort, exposure to $PM_{2.5}$ and NO_2 in the first trimester was associated with the risk of noncritical heart defects, particularly atrial septal defects. There was evidence of a possible association with critical heart defects, including coarctation of the aorta, although the prevalence of these anomalies was low. The association with heart defects was greater in women with comorbidity. Women with anemia who were exposed to higher levels of pollution were more likely to have fetal heart defects. Women with epilepsy or mood disorders, hypertensive disorders, and preeclampsia who were exposed to pollution also tended to have a greater risk of fetal heart defects, although power was limited for these comorbidities. This study suggests that prenatal exposure to air pollution may increase the risk of noncritical heart defects, particularly in susceptible women.

Table 4. Association of ambient $PM_{2.5}$ and NO_2 in the month of conception and first trimester of pregnancy with risk of any heart defect, Quebec (Canada), 2000–2016.

	OR per IQR increment (95% CI)[a]	
	$PM_{2.5}$	NO_2
Monthly average in first trimester		
Single-pollutant model	1.02 (1.00, 1.05)	1.10 (1.07, 1.13)
Two-pollutant model	0.98 (0.95, 1.00)	1.11 (1.08, 1.15)
Monthly average at conception		
Single-pollutant model	1.01 (0.99, 1.04)	1.10 (1.07, 1.13)
Two-pollutant model	0.98 (0.96, 1.00)	1.11 (1.08, 1.15)

Note: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm.
[a]Logistic regression models for 1-IQR change in air pollutant levels, adjusted for maternal age, parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, maternal comorbidity, and season of conception. IQR increments are 3.3 $\mu g/m^3$ for ambient $PM_{2.5}$ and 11.4 ppb for ambient NO_2.

Table 5. Association between ambient $PM_{2.5}$ and NO_2 in the first trimester of pregnancy and odds of critical and noncritical heart defects, Quebec (Canada), 2000–2016.

	Defects (n)	OR per IQR increment (95% CI)[a]	
		$PM_{2.5}$	NO_2
Noncritical heart defect			
Any	12,053	1.03 (1.00, 1.05)	1.11 (1.08, 1.14)
Ventricular septal defect	4,332	0.94 (0.90, 0.98)	1.00 (0.95, 1.05)
Atrial septal defect	3,136	1.08 (1.03, 1.14)	1.18 (1.12, 1.25)
Critical heart defect			
Any	1,400	1.01 (0.94, 1.09)	0.97 (0.89, 1.06)
Tetralogy of Fallot	345	1.04 (0.89, 1.22)	0.93 (0.77, 1.11)
Coarctation of the aorta	343	1.02 (0.87, 1.19)	1.10 (0.92, 1.31)

Note: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm.
[a]Single-pollutant logistic regression models for 1-IQR change in air pollutant levels, adjusted for maternal age, parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, maternal comorbidity, and season of conception. IQR increments are 3.3 $\mu g/m^3$ for ambient $PM_{2.5}$ and 11.4 ppb for ambient NO_2.

The mechanisms by which air pollution may lead to heart defects have yet to be established. Congenital heart defects arise in the first trimester during migration and differentiation of neural crest cells, and septation of the primordial heart into the atrial and ventricular compartments.[46] Because cardiogenesis begins shortly after conception, with the heart continuing to form throughout the first trimester, exposures that affect cardiac development in the first trimester may be more important than exposures at conception alone. In particular, first trimester exposures that interrupt septation may result in incomplete or partial closure of the primary atrial foramen or secondary atrial septum, leading to atrial septal defects.[27] Ventricular septal defects may develop following disruption in transcription of genes that code for growth factors involved in forming the outflow tract and atrioventricular canal.[46] Pollutants may interfere in cardiogenesis by causing placental inflammation and oxidative stress, and generating reactive oxygen and nitrogen species that alter DNA and mRNA expression.[47] Another hypothesis is that air pollutants impede the normal migration of neural crest cells into the heart.[43] Epigenetic mechanisms are also thought to be involved.[47]

However, epidemiological studies of heart defects have provided only mixed support for these pathways, in addition to being limited in number and lacking power. In the largest review and meta-analysis of air pollution and congenital heart defects, NO_2 and $PM_{2.5}$ exposures were not associated with atrial septal defects[16]; meta-estimates of associations were 0.98 (95% CI: 0.90, 1.06) per 10-ppb increase in NO_2 and 1.08 (95% CI: 0.87, 1.34) per 10-$\mu g/m^3$ increase in $PM_{2.5}$. These meta-estimates derived from positive associations reported in 4[9,48–50] of 10 studies[6–9,11,32,48–51] for NO_2, and in 3[7,9,52] of 5 studies[7,9,11,32,52] for $PM_{2.5}$. In our analysis, both $PM_{2.5}$ and NO_2 were associated with a greater risk of atrial septal defects at term. A potential source of heterogeneity in findings could relate to the process of cardiogenesis. The atrium starts forming in the fifth gestational week and continues to mature in the second and third trimesters before closing.[27] In preterm infants, atrial septal defects are due to physiological immaturity and are not pathological.[53] Preterm atrial septal defects were excluded from our analyses; however, to our knowledge, previous studies included preterm births.

Table 6. Association between exposure to $PM_{2.5}$ and NO_2 in the first trimester of pregnancy and congenital heart defects in 1,342,198 newborns born to women with and without comorbidity in Quebec (Canada), 2000–2016.

		$PM_{2.5}$		NO_2	
	Defects (*n*)	OR per IQR increment (95% CI)[a]	Cochran's Q *p*-value	OR per IQR increment (95% CI)[a]	Cochran's Q *p*-value
Any comorbidity			<0.001		<0.001
Yes	3,013	1.11 (1.06, 1.17)		1.23 (1.17, 1.31)	
No	9,702	0.99 (0.97, 1.02)		1.06 (1.03, 1.09)	
Obesity			0.24		0.22
Yes	417	0.93 (0.81, 1.09)		0.96 (0.78, 1.19)	
No	12,298	1.02 (1.00, 1.05)		1.10 (1.07, 1.13)	
Preexisting diabetes (type 1 or 2)			0.61		0.13
Yes	429	1.05 (0.91, 1.21)		0.97 (0.83, 1.14)	
No	12,286	1.02 (1.00, 1.05)		1.09 (1.06, 1.12)	
Preeclampsia			0.38		0.08
Yes	719	1.07 (0.95, 1.19)		1.21 (1.08, 1.36)	
No	11,996	1.02 (0.99, 1.04)		1.09 (1.06, 1.12)	
Preexisting hypertension			0.03		0.48
Yes	340	1.20 (1.03, 1.41)		1.15 (0.96, 1.36)	
No	12,375	1.01 (0.99, 1.04)		1.09 (1.06, 1.12)	
Epilepsy and mood disorders			0.12		0.03
Yes	119	1.24 (0.95, 1.62)		1.54 (1.13, 2.10)	
No	12,596	1.01 (0.99, 1.04)		1.09 (1.06, 1.12)	
Anemia			<0.001		<0.001
Yes	1,476	1.21 (1.13, 1.31)		1.28 (1.18, 1.38)	
No	11,239	0.99 (0.96, 1.02)		1.06 (1.02, 1.09)	
Substance use disorder			0.86		0.23
Yes	273	1.01 (0.85, 1.20)		0.96 (0.77, 1.20)	
No	12,442	1.02 (1.00, 1.05)		1.09 (1.06, 1.13)	

Note: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; OR, odds ratio; $PM_{2.5}$, fine particulate matter of aerodynamic diameter <2.5 μm.
[a]Single-pollutant logistic regression model for 1-IQR change in air pollutant levels, adjusted for maternal age, parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, and season of conception. IQR increments are 3.3 $\mu g/m^3$ for ambient $PM_{2.5}$ and 11.4 ppb for ambient NO_2.

For ventricular septal defects, our findings showed null or negative associations, which is consistent with most previous studies.[7,11,14,32,50,51] In one meta-analysis, the pooled effect estimates were 1.04 (95% CI: 0.87, 1.25; $n = 5$ studies) for a 10-$\mu g/m^3$ increase in $PM_{2.5}$ and 0.97 (95% CI: 0.91, 1.44; $n = 11$ studies) for a 10-ppb increase in NO_2.[16] Although restriction to live-born infants could explain the absent or inverse association we found with ventricular septal defects, a large numbers of terminations would need to be missing differentially in terms of exposure to induce a sufficiently large bias.[35,54] Moreover, adjustment for maternal comorbidities and other covariates that are common causes of heart defects and fetal loss may have helped minimize live-birth bias.[35,36]

Analyses of critical heart defects suggest that $PM_{2.5}$ and NO_2 may increase the risk of tetralogy of Fallot and coarctation of the aorta. Despite having more cases than in any previous studies, prevalence of these anomalies remained low, resulting in wider CIs. A meta-analysis appears to support the possibility that NO_2 exposure increases the risk of tetralogy of Fallot (pooled OR = 1.11; 95% CI: 0.95, 1.30) and coarctation of the aorta (pooled OR = 1.12; 95% CI: 0.99, 1.18).[16] However, individual studies have provided inconsistent results in terms of direction of the association. For $PM_{2.5}$, positive associations with tetralogy of Fallot have been reported in most studies,[7,9,11,13] resulting in a meta-estimate of 1.12 (95% CI: 0.98, 1.28) per 10-$\mu g/m^3$ increment in $PM_{2.5}$.[16]

The modifying role of maternal comorbidity remains poorly understood. Prior studies have paid limited attention to comorbidity. In China, an analysis of 61,884 women exposed to NO_2 suggested that risks of heart defects were greater in women with higher prepregnancy body mass index, diabetes, or thyroid disease.[40] Our analysis of >1.3 million women with 12,700 heart defects indicates that comorbidity may be a modifier. $PM_{2.5}$ and NO_2 had a greater association with heart defects in children born to women with anemia, epilepsy and mood disorders, preeclampsia, and preexisting hypertension. Associations with heart defects were most prominent for anemia, a hematologic disorder closely linked with cardiac development. Embryonic hypoxia due to anemia is associated with abnormal angiogenesis, placental oxidative stress, and inflammation through reactive oxygen species.[55] Reduced iron intake is associated with increased risk of congenital heart defects in pregnant women, and NO_2 and $PM_{2.5}$ are associated with anemia in adults.[56,57] Similarly, preeclampsia and hypertension may lead to endothelial dysfunction that modifies the impact of pollutants on the developing heart.[55] Maternal hypertension is associated with uteroplacental insufficiency, fetal cardiac vascular dysfunction, and cell death, which are common mechanisms linking pollution with heart defects.[37,47] Both preeclampsia and hypertension are associated with an increased risk of heart defects.[37,38] Patients with epilepsy and psychiatric disorders may be susceptible given that they may be treated with medications that are potentially teratogenic.[58]

In general, NO_2 was more strongly associated with heart defects than $PM_{2.5}$. NO_2 is mainly emitted by road traffic and industrial burning and is a marker of traffic pollution in urban areas.[59] In contrast, ambient $PM_{2.5}$ is a heterogenous mixture that may make associations with heart defects harder to detect. Nevertheless, both pollutants were more strongly associated with heart defects in Montreal, where road traffic is greater. Associations may be attenuated in rural areas where postal codes are larger, thus contributing to exposure misclassification.

Most prior studies used routine fixed monitoring stations to assign exposures based on the nearest monitor[6,8,13,14,33,48,49] or the average (or distance-weighted average) of measurements at multiple stations in the study area or within a subjectively defined cutoff distance from the residence.[3,15,32,50] Monitoring sites could be as far as 30 or 50 km from the residence.[3,50] These exposure assessment methods do not adequately capture spatial variation in $PM_{2.5}$ and NO_2 concentrations, causing considerable exposure misclassification for spatially heterogenous pollutants such as NO_2. In contrast, we used air pollution exposure estimates that captured both spatial and temporal variation.

We had high coverage of heart defects, but did not include stillbirths, and did not have data for miscarriages, terminations, and stillbirths, or heart defects detected later in childhood. There may be uncertainty in conception dates, but analyses of correlated windows of exposure yielded similar results. We had monthly exposure data and thus could not assess exposures specifically between weeks 3 and 8 of gestation, the period when heart defects form. However, we do not expect an influence on estimated associations given that exposures during the month of conception and first trimester were strongly correlated and yielded similar estimates of association. We could not account for movement or activity patterns that may attenuate estimates.[60] We adjusted for a number of risk factors, but cannot rule out residual confounding from unmeasured risk factors, such as family history, or pharmacotherapy.

In this large population-based cohort study, maternal exposure to $PM_{2.5}$ and NO_2 in the first trimester was associated with an increased risk of noncritical heart defects, particularly atrial septal defects. Mothers with comorbidities, particularly anemia, epilepsy and mood disorders, preeclampsia, and preexisting hypertension were more susceptible. Further studies addressing the role of maternal comorbidity are needed to consolidate our findings. Future work should also aim to establish critical windows of exposure and the exact pathways affecting fetal heart development.

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