

**Note to readers with disabilities:** *EHP* strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in *EHP* articles may not conform to [508 standards](#) due to the complexity of the information being presented. If you need assistance accessing journal content, please contact [ehp508@niehs.nih.gov](mailto:ehp508@niehs.nih.gov). Our staff will work with you to assess and meet your accessibility needs within 3 working days.

### **Supplemental Material**

#### **Association between First Trimester Exposure to Ambient PM<sub>2.5</sub> and NO<sub>2</sub> and Congenital Heart Defects: A Population-Based Cohort Study of 1,342,198 Live Births in Canada**

Stéphane Buteau, Paige Veira, Marianne Bilodeau-Bertrand, and Nathalie Auger

#### **Table of Contents**

**Table S1.** Pearson correlation coefficient between different windows of exposure to ambient PM<sub>2.5</sub> and NO<sub>2</sub> in a cohort of 1,342,198 newborns born to women in Quebec (Canada), 2000-2016.

**Table S2.** Distribution of exposures to ambient PM<sub>2.5</sub> and NO<sub>2</sub> for the whole cohort (N=1,342,198) and for those living in Montreal (N=359,423) in the month of conception and first trimester, 2000-2016.

**Table S3.** Model fit of adjusted response function for first trimester exposure to air pollutants using linear and nonlinear structures in the association with congenital heart defects among 1,342,198 newborns in Quebec (Canada), 2000-2016.

**Table S4.** Association between heart defect and ambient PM<sub>2.5</sub> and NO<sub>2</sub> in the first trimester of pregnancy among newborns with a single heart defect, Quebec (Canada), 2000-2016.

**Table S5.** Adjusted odds ratio between air pollution exposure in the first trimester of pregnancy and congenital heart defects in 1,342,198 newborns in Quebec, according to residency and season of conception, 2000-2016.

**Figure S1.** Conceptual directed acyclical graph (DAG) for first trimester outdoor PM<sub>2.5</sub>/NO<sub>2</sub> concentrations and congenital heart defect.

**Figure S2.** Concentration-response function for the association of congenital heart defects with first trimester exposure to ambient (A) PM<sub>2.5</sub> and (B) NO<sub>2</sub> fitted using restricted cubic splines with three degrees of freedom.

**Figure S3.** Adjusted response function for maternal age in the association between congenital heart defects with first trimester exposure to ambient (A) PM<sub>2.5</sub> and (B) NO<sub>2</sub>.

## Tables

**Table S1.** Pearson correlation coefficient between different windows of exposure to ambient PM<sub>2.5</sub> and NO<sub>2</sub> in a cohort of 1,342,198 newborns born to women in Quebec (Canada), 2000-2016

	PM <sub>2.5</sub>		NO <sub>2</sub>	
	Trimester 1	Month of conception	Trimester 1	Month of conception
PM <sub>2.5</sub>				
First trimester	1.00			
Month of conception	0.81	1.00		
NO <sub>2</sub>				
First trimester	0.59	0.48	1.00	
Month of conception	0.58	0.52	0.97	1.00

Abbreviations: NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, fine particulate matter of aerodynamic diameter < 2.5 µm.

**Table S2.** Distribution of exposures to ambient PM<sub>2.5</sub> and NO<sub>2</sub> for the whole cohort

(N=1,342,198) and for those living in Montreal (N=359,423) in the month of conception and first trimester, 2000-2016.

	Mean	SD	Percentile					IQR
			5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>	
PM <sub>2.5</sub> (µg/m <sup>3</sup> )								
Whole cohort								
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
Montreal								
First trimester	9.7	2.0	7.1	8.3	9.4	10.9	13.4	2.6
Month of conception	9.6	2.8	6.0	7.6	9.3	11.1	14.3	3.5
NO <sub>2</sub> (ppb)								
Whole cohort								
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
Montreal								
First trimester	20.7	8.4	9.4	14.3	19.5	25.7	36.0	11.4
Month of conception	20.6	8.9	9.1	13.9	19.2	25.8	37.1	11.9

Abbreviations: IQR, interquartile range; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, fine particulate matter of aerodynamic diameter < 2.5 µm;

SD, standard deviation.

**Table S3.** Model fit of adjusted response function for first trimester exposure to air pollutants using linear and nonlinear structures in the association with congenital heart defects among 1,342,198 newborns in Quebec (Canada), 2000-2016<sup>1</sup>

Functional form of air pollutant	Akaike information criterion	
	PM <sub>2.5</sub>	NO <sub>2</sub>
Linear	135,055	140,333
Natural cubic splines, 3 df	135,048	140,329

Abbreviations: df, degrees of freedom; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, fine particulate matter of aerodynamic diameter < 2.5 μm.

<sup>1</sup>Single pollutant logistic regression models, adjusted for maternal age (natural splines, 3 df), parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, maternal comorbidity and season of conception.

**Table S4.** Association between heart defect and ambient PM<sub>2.5</sub> and NO<sub>2</sub> in the first trimester of pregnancy among newborns with a single heart defect, Quebec (Canada), 2000-2016

	No. defects	Odds ratio per IQR (95% CI) <sup>a</sup>	
		PM <sub>2.5</sub>	NO <sub>2</sub>
Any heart defect	10,123	1.01 (0.98, 1.04)	1.06 (1.03, 1.09)
Noncritical heart defect			
Any	9,484	1.01 (0.98, 1.04)	1.07 (1.04, 1.11)
Ventricular septal defect	3,105	0.92 (0.87, 0.96)	0.96 (0.90, 1.01)
Atrial septal defect	1,531	1.03 (0.96, 1.11)	1.16 (1.08, 1.24)
Critical heart defect			
Any	639	0.94 (0.84, 1.06)	0.89 (0.79, 1.01)
Tetralogy of Fallot	224	0.99 (0.82, 1.20)	0.83 (0.67, 1.03)
Coarctation of the aorta	149	1.03 (0.81, 1.31)	1.09 (0.86, 1.39)

Abbreviations: CI, confidence interval; IQR, interquartile range; NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, fine particulate matter of aerodynamic diameter < 2.5 μm.

<sup>a</sup>Single-pollutant logistic regression models for one interquartile 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. Interquartile range increments are 3.3 μg/m<sup>3</sup> for ambient PM<sub>2.5</sub> and 11.4 ppb for ambient NO<sub>2</sub>.

**Table S5.** Adjusted odds ratio between air pollution exposure in the first trimester of pregnancy and congenital heart defects in 1,342,198 newborns in Quebec, according to residency and season of conception, 2000-2016.

Characteristics	PM <sub>2.5</sub>		NO <sub>2</sub>	
	Odds ratio per interquartile increment (95% confidence interval) <sup>1</sup>	Cochran's Q p-value	Odds ratio per interquartile increment (95% confidence interval) <sup>1</sup>	Cochran's Q p-value
Urban residence <sup>2</sup>		0.02		0.86
Yes	1.03 (1.00, 1.16)		1.10 (1.07, 1.13)	
No	0.94 (0.88, 1.01)		1.12 (0.79, 1.59)	
Montreal <sup>2</sup>		0.01		<0.001
Yes	1.03 (0.98, 1.09)		1.13 (1.06, 1.20)	
No	0.98 (0.95, 1.01)		0.97 (0.92, 1.02)	
Season of conception <sup>3</sup>		0.60		<0.001
Winter	1.03 (0.98, 1.08)		1.10 (1.05, 1.15)	
Spring	1.05 (0.99, 1.12)		1.22 (1.13, 1.31)	
Summer	1.01 (0.95, 1.08)		1.07 (0.99, 1.15)	
Fall	1.00 (0.96, 1.05)		1.06 (1.02, 1.12)	

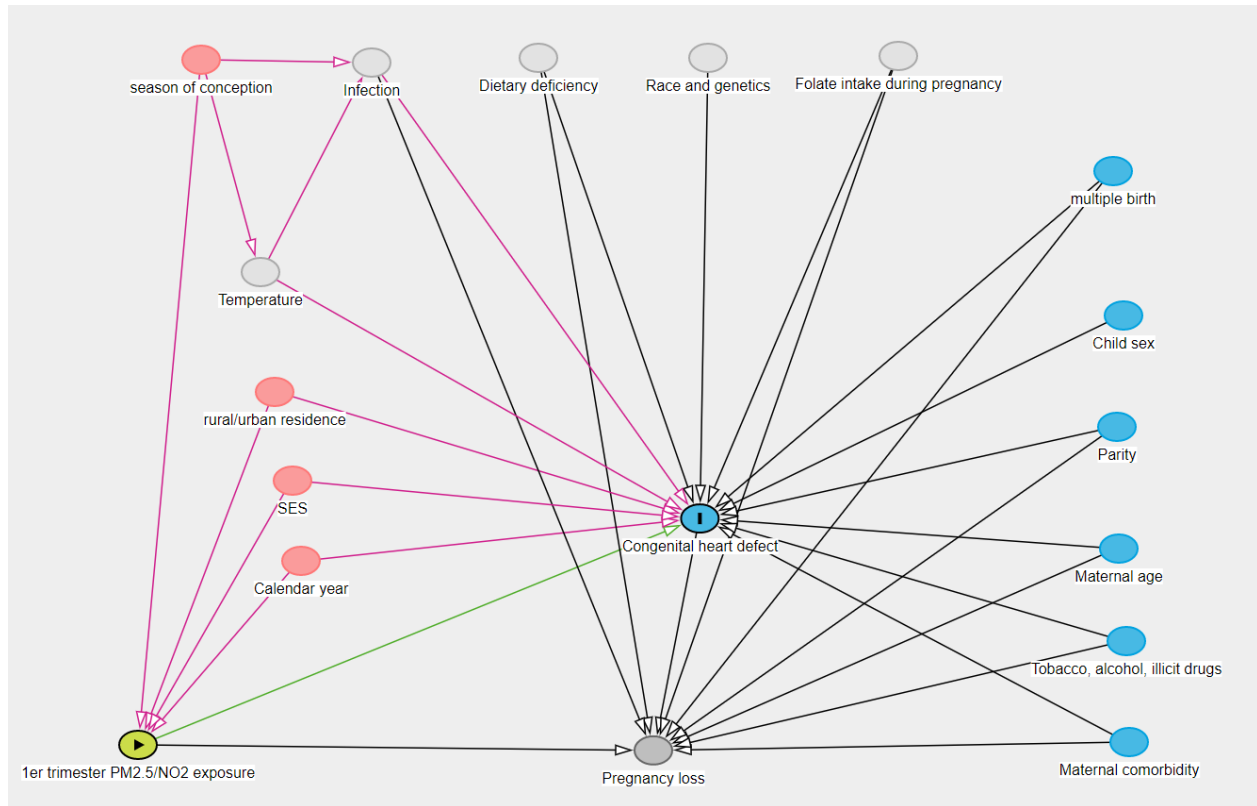
Abbreviations: NO<sub>2</sub>, nitrogen dioxide; PM<sub>2.5</sub>, fine particulate matter of aerodynamic diameter <2.5 µm.

<sup>1</sup>Interquartile range increments are 3.3 µg/m<sup>3</sup> for ambient PM<sub>2.5</sub> and 11.4 ppb for ambient NO<sub>2</sub>.

<sup>2</sup>Single-pollutant model adjusted for maternal age, parity, sex, multiple birth, material deprivation, birth year and season of conception.

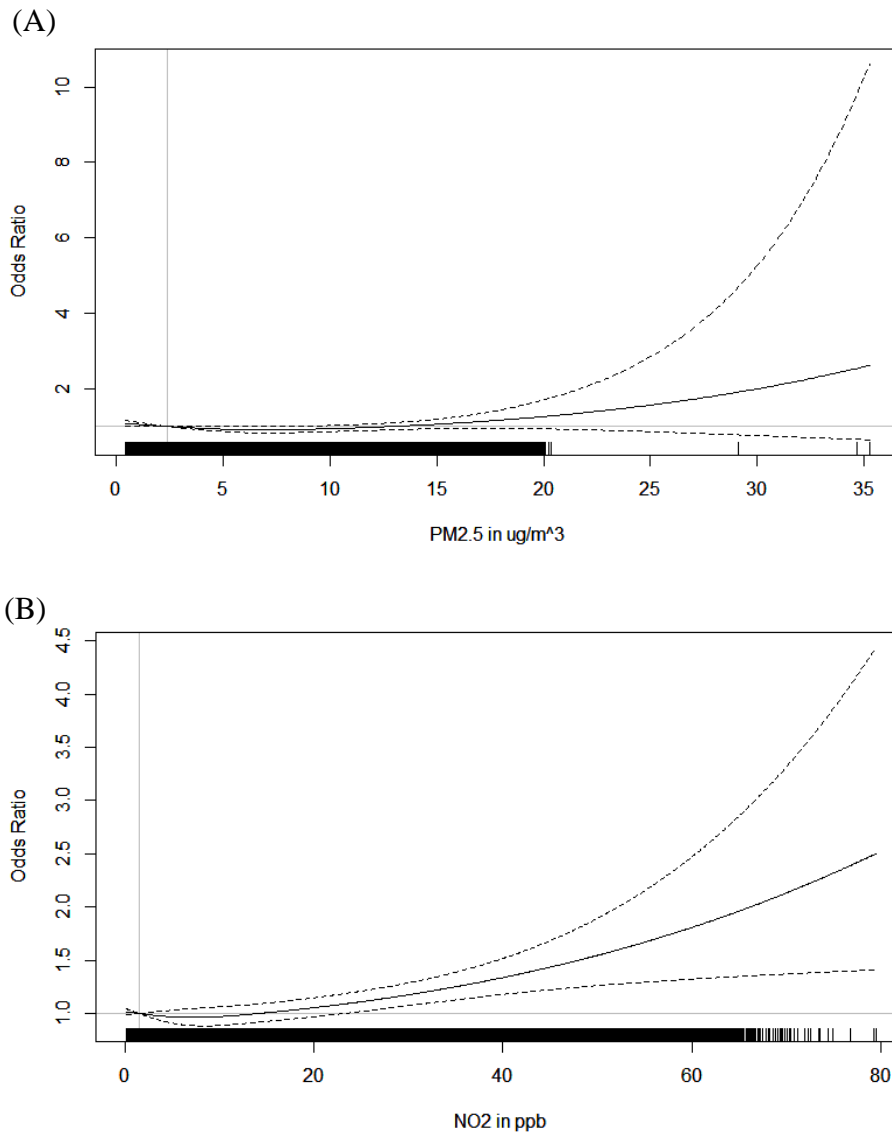
<sup>3</sup>Single-pollutant model adjusted for maternal age, parity, sex, multiple birth, material deprivation, birth year, rural/urban residence.

## Figures



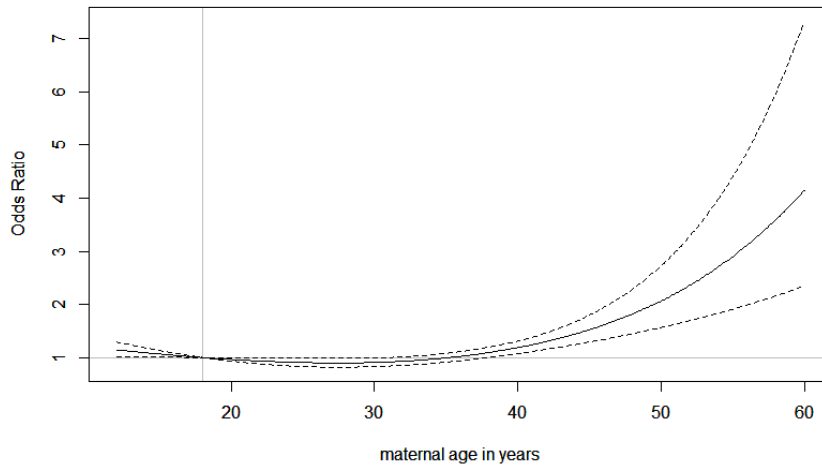
**Figure S1. Conceptual directed acyclical graph (DAG) for first trimester outdoor PM<sub>2.5</sub>/NO<sub>2</sub> concentrations and congenital heart defect.** Parameters in grey are unmeasured variables, parameters in red are potential confounding factors, and parameters in blue are other risk factors considered in logistic regression models.



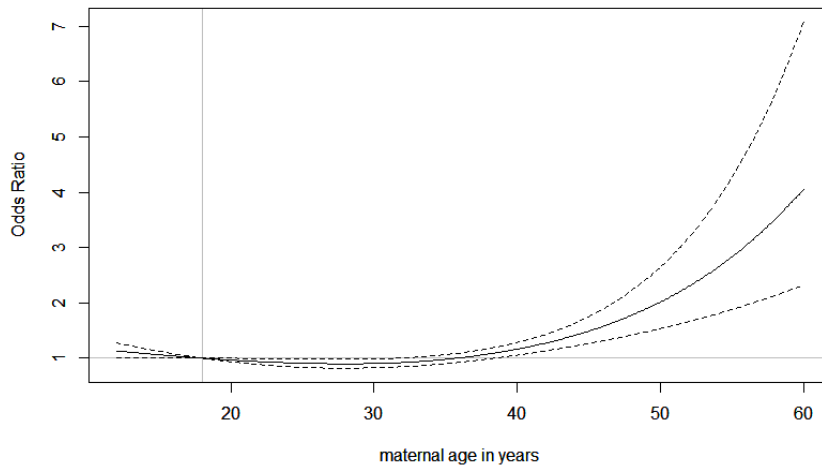


**Figure S2. Concentration-response function for the association of congenital heart defects with first trimester exposure to ambient (A) PM<sub>2.5</sub> and (B) NO<sub>2</sub> fitted using restricted cubic splines with three degrees of freedom.** The solid line represents the mean adjusted odds ratio, with dashed lines representing 95% confidence intervals from a single pollutant logistic regression model adjusted for maternal age, parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, maternal comorbidity, and season of conception. The rug plot above the horizontal axis shows the distribution of air pollutants. The ORs are relative to the 1<sup>st</sup> percentile of the exposure distribution (i.e., 2.4  $\mu\text{g}/\text{m}^3$  for PM<sub>2.5</sub>, 1.5 ppb for NO<sub>2</sub>). For PM<sub>2.5</sub>, ORs at 25<sup>th</sup> (6.3  $\mu\text{g}/\text{m}^3$ ), 75<sup>th</sup> (9.6  $\mu\text{g}/\text{m}^3$ ) and 95<sup>th</sup> (12.4  $\mu\text{g}/\text{m}^3$ ) percentiles are 0.90 (95% CI: 0.82, 0.99), 0.93 (95% CI: 0.85, 1.01) and 0.99 (95% CI: 0.90, 1.08). For NO<sub>2</sub>, ORs at 25<sup>th</sup> (4.6 ppb), 75<sup>th</sup> (16.0 ppb) and 95<sup>th</sup> (28.8 ppb) percentiles are 0.96 (95% CI: 0.91, 1.01), 1.00 (95% CI: 0.92, 1.07) and 1.13 (95% CI: 1.04, 1.22).

(A)



(B)



**Figure S3. Adjusted response function for maternal age in the association between congenital heart defects with first trimester exposure to ambient (A)  $PM_{2.5}$  and (B)  $NO_2$ .** The solid line represents the mean adjusted odds ratio (OR) for maternal age fitted using restricted cubic splines with three degrees of freedom, with dashed lines representing 95% confidence intervals (CI) from a single pollutant logistic regression model adjusted for parity, sex, multiple birth, material deprivation, birth year, rural/urban residence, maternal comorbidity, and season of conception. The ORs are relative to the 1<sup>st</sup> percentile of maternal age (i.e., 18 years). ORs at 25<sup>th</sup> (26 years), 75<sup>th</sup> (33 years) and 95<sup>th</sup> (38 years) percentiles are 0.90 (95% CI: 0.82, 0.99), 0.95 (95% CI: 0.87, 1.03) and 1.09 (95% CI: 1.00, 1.19) in Figure S3A, and 0.90 (95% CI: 0.83, 0.99), 0.94 (95% CI: 0.86, 1.02) and 1.08 (95% CI: 0.99, 1.17) in Figure S3B.