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Spatial variations in ambient ultrafine particle concentrations and risk of congenital heart defects

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ABSTRACT

Background: Cardiovascular malformations account for nearly one-third of all congenital anomalies, making these the most common type of birth defects. Little is known regarding the influence of ambient ultrafine particles (< 0.1 μm) (UFPs) on their occurrence.

Objective: This population-based study examined the association between prenatal exposure to UFPs and congenital heart defects (CHDs).

Methods: A total of 158,743 singleton live births occurring in the City of Toronto, Canada between April 1st 2006 and March 31st 2012 were identified from a birth registry. Associations between exposure to ambient UFPs between the 2nd and 8th week post conception when the foetal heart begins to form and CHDs identified at birth were estimated using random-effects logistic regression models, adjusting for personal- and neighbourhood-level covariates. We also investigated multi-pollutant models accounting for co-exposures to $PM_{2.5}$, NO_2 and O_3.

Results: A total of 1468 CHDs were identified. In fully adjusted models, UFP exposures during weeks 2 to 8 of pregnancy were not associated with overall CHDs (Odds Ratio (OR) per interquartile (IQR) increase = 1.02, 95% CI: 0.96–1.08). When investigating subtypes of CHDs, UFP exposures were associated with ventricular septal defects (Odds Ratio (OR) per interquartile (IQR) increase = 1.13, 95% CI: 1.03–1.33), but not with atrial septal

Abbreviations: OR, odds ratio; CI, confidence interval; UFPs, ultrafine particles; $PM_{2.5}$, particulate matter with a mean aerodynamic diameter < 2.5 μm; NO_2, nitrogen dioxide; O_3, ozone; CHD, congenital heart defect

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defect (Odds Ratio (OR) per interquartile (IQR) increase = 0.89, 95% CI: 0.74–1.06).
Conclusion: This is the first study to evaluate the association between prenatal exposure to UFPs and the risk of CHDs. UFP exposures during a critical period of embryogenesis were associated with an increased risk of ventricular septal defect.

1. Introduction

Congenital heart defects (CHDs) are associated with significant societal costs and are a leading cause of infant morbidity and mortality (Avila et al., 2014; Oster et al., 2013). Cardiovascular malformations account for nearly one-third of all congenital anomalies, making these the most common type of birth defects (van der Linde et al., 2011). While the specific causes of cardiac malformations have not been clearly identified, previous research has suggested that prenatal exposure to ambient air pollution is associated with their development (Huang et al., 2019; Hwang et al., 2015; Liu et al., 2017; Ren et al., 2018; Schembari et al., 2014; Stingone et al., 2017; Vrijheid et al., 2011; Zhang et al., 2016a; Zhang et al., 2016b; Zhang et al., 2018). Most studies have focused on criteria pollutants such as particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3), but there remains considerable uncertainty whether these pollutants are primarily responsible for the observed adverse effects. There is increasing interest in ultrafine particles ($\leq$ 0.1 μm in diameter; UFPs) which are produced in large numbers by diesel vehicles and other combustion processes (HEI Review Panel on Ultrafine Particles, 2013), but little is known regarding the impact of UFPs on fetal cardiovascular malformations.

The relationship of ambient air pollution with risks of CHDs has been investigated in several previous studies, with associations mainly reported for coarctation of the aorta, tetralogy of Fallot, atrial septal defect and ventricular septal defect (Huang et al., 2019; Hwang et al., 2015; Liu et al., 2017; Ren et al., 2018; Schembari et al., 2014; Stingone et al., 2017; Vrijheid et al., 2011; Zhang et al., 2016a; Zhang et al., 2016b; Zhang et al., 2018). A meta-analysis found an association between particulate matter ($<$ 10 μm) (PM_{10}) and atrial septal defect (Vrijheid et al., 2011). Other more recent studies found inconsistent associations between $PM_{2.5}$ and specific types of CHDs (Huang et al., 2019; Padula et al., 2013; Schembari et al., 2014; Stingone et al., 2017; Zhang et al., 2016a). Recent experimental studies conducted in mice suggests that smaller size particles, such as UFPs, could be responsible for PM-induced cardiac defects through oxidative stress, DNA damage, and alteration of molecular signalling or epigenetic events (Teng et al., 2016). Therefore, it is important to evaluate the possible impact of UFPs on foetal cardiac development.

In the present study, we examined the association between UFP exposures during the early weeks of pregnancy and CHDs using a population-based cohort study in Toronto, Canada. We also evaluated if ambient UFPs are independently associated with CHDs after adjusting for major ambient air pollutants, namely particulate matter with aerodynamic diameters of $\leq$2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3).

2. Methods

2.1. Study population and design

We used a retrospective cohort of pregnant women giving birth to live born singleton infants between April 1st 2006 and March 31st 2012 in Toronto, Canada. Mother-infant pair data were obtained from the Better Outcomes Registry & Network (BORN) Ontario database (http://www.bornontario.ca). Gestational age was determined from the mother's last menstrual period and ultrasound dating. In particular, for every mother-infant pair we identified the period between the 2nd and 8th week post conception, based on previous studies (Agay-Shay et al., 2013; Auger et al., 2017; Ren et al., 2018; Stingone et al., 2017), in order to focus on the gestational period when the foetal heart begins to form (Moorman et al., 2003).

Postal Code Conversion File Plus (PCCF+) software was used to obtain the geographic coordinates of maternal place(s) of residence during the critical period of exposure based on residential postal code (s) reported in health administrative data. Maternal residential 6-digit postal code(s) during pregnancy were obtained from the Registered Persons Database (RPDB), which contains annual demographic information on Ontario residents. This database also records postal code changes which have been reported to the Ministry of Health for all Ontario residents who have ever had a health insurance number. It contains the postal code, a start and end date defining the period during which the postal code applied to the subscriber. For each year, using July 1st as a reference point, the best known postal code address is captured using the latest postal code reported across health administrative databases in the 1st half of each year or else the earliest one identified in the 2nd half of each year. Therefore, this database can capture to some extent postal code changes during pregnancy and therefore assign exposures accordingly. The housing and linkage of the administrative data sources was conducted at ICES in Ontario, Canada. ICES uses encrypted unique identifiers based on universal health insurance numbers to be able to accurately gather information on individuals across these different data sources. Subjects were excluded if they had a residential postal code outside Toronto, a missing postal code, a missing health card number, a missing date of birth and/or missing information on sex.

2.2. Ascertainment of congenital heart defects

We obtained CHD outcomes after linking mother-infant pair data to hospitalisation data from the Hospital Discharge Abstract Database (DAD) of the Canadian Institute of Health Information. We identified CHDs from birth to one year of age. Ontario, the most populous province in Canada, has a publicly funded universal medicare system for hospital, laboratory, and physician services that covers the whole population, including all hospital births in Ontario. We identified cases with any major CHDs (International Classification of Diseases [ICD]-10: Q20–Q26) as well as seven major subtypes: transposition of great vessels (ICD-10 code: Q203), ventricular septal defect (ICD-10 code: Q210), atrial septal defect (ICD-10 code: Q211), atrioventricular defect (ICD-10 code: Q212), tetralogy of Fallot (ICD-10 code: Q213), tricuspid atresia and stenosis (ICD-10 code Q224), pulmonary valve stenosis (ICD-10 code Q221) and coarctation of aorta (ICD-10 code: Q251) (Huang et al., 2019; Schembari et al., 2014). Here we focus mainly on overall CHDs, ventricular septal defect and atrial septal defect because too few cases ($<$ 20) were available for the other subtypes. We excluded births with chromosomal abnormalities. Defects were diagnosed based on ultrasound examinations in utero or postnatally before discharge from hospital. The CHD diagnoses were identified on the infant's hospital discharge abstract and linkage between DAD and BORN was performed using encrypted unique identifiers which is the standard approach in linking health administrative data within the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada.

2.3. Exposure assessment for ambient air pollutants

Air pollution exposure estimates were assigned to the geographical coordinates representing the centroid of each mother's residential 6-digit postal codes of residence(s) during weeks 2 to 8 of pregnancy. In

Toronto, 6-digit postal codes are generally represented by one side of a city block or a large apartment complex. We assigned residential exposure to ambient UFPs derived from a land use regression (LUR) model developed using mobile monitoring data collected for two weeks in the summer (September 2010) and one week in the winter (March 2011) including data from 405 road segments distributed across the city of Toronto (Weichenthal et al., 2016a). In brief, the monitoring was conducted using 3 separate vehicles equipped with rooftop monitoring devices (TSI model 3007; TSI Inc., Shoreview, Minnesota) measuring real-time ambient UFPs at 1-s resolution. The terms in the LUR model include the logarithm of distances to highways, major roads, the central business district, Toronto Pearson International Airport, and bus routes. The LUR model also includes variables for the numbers of on-street trees, parks and open spaces, the length of bus routes within a 100-m buffer, as well as linear and quadratic terms for ambient temperature which were found to be important determinants of temporal variations in ambient UFPs (Alm et al., 1999; Kaur and Nieuwenhuijsen, 2009; Weichenthal et al., 2016a; Weichenthal et al., 2016b). The final model explained 67% of the variation in mean UFPs. In order to account for the temporal variations to UFPs, we incorporated weekly average ambient temperature in our UFPs LUR model. Weekly temperature surfaces for the study period were obtained at the 6-digit postal code resolution for the city of Toronto. The surfaces were provided by the Canadian Urban Environmental Health Research Consortium (CANUE) and were developed by the Canadian Forest Service of Natural Resources Canada (Canadian Forest Service of Natural Resources Canada October, 2017; DMTI Spatial Inc., 2015). The resulting temporally adjusted UFP exposures were linked to weeks 2 to 8 of pregnancy for each mother-infant pair (Lavigne et al., 2019).

We used different methods to reconstruct exposures to the different pollutants investigated in this study. We assigned exposure to $PM_{2.5}$ during weeks 2 to 8 of pregnancy, based on a long-term satellite surface at a 1 × 1 km resolution (van Donkelaar et al., 2015) temporally scaled, using previously detailed methods (Bechle et al., 2015; Lavigne et al., 2018), in order to obtain weekly exposures to $PM_{2.5}$ across the study period. Exposure to ambient NO_2 was based on a LUR model derived from a monitoring campaign of ground-level concentrations of NO_2 conducted in the City of Toronto (Jerrett et al., 2007). Concentrations of exposure to O_3 using 21 km grid values were also assigned to the 6-character postal codes based on a surface representing the average of the daily 8-h maximum concentrations in the warm seasons (May 1st to October 31st) for the period of 2002 to 2009 across Canada (Crouse et al., 2015; Robichaud and Ménard, 2014).

The temporal adjustment applied to the satellite-derived $PM_{2.5}$ estimates, LUR NO_2 model and O_3 surface allowed to more precisely identify exposures on a weekly basis during weeks 2 to 8 of pregnancy (Lavigne et al., 2018). This was done by first generating scaling factors by calculating a ratio of weekly mean $PM_{2.5,}$ NO_2 and O_3 concentrations for each ground monitor in the City of Toronto to the long-term concentrations for each of these monitor locations. The ambient concentrations of $PM_{2.5,}$ NO_2 and O_3 at each fixed-site monitor locations were obtained from Environment Canada. Scaling surfaces were then created for each week of the study period by applying inverse distance weighting (IDW) spatial interpolation methods for each postal code located within 25 km of a ground monitor. The weekly $PM_{2.5,}$ NO_2 and O_3 surface concentrations were obtained by applying the scaling surfaces to the long-term estimates (Bechle et al., 2015). Weekly surfaces were then used to estimate exposures during weeks 2 to 8 of pregnancy.

2.4. Covariates

Potential confounders in this study that were available from the birth registry included maternal age at delivery (< 20, 20–34, ≥ 35), maternal self-reported cigarette smoking anytime during pregnancy (yes, no or unknown), maternal alcohol consumption during pregnancy (yes, no or unknown), maternal body mass index (BMI) (< 25.0, 25.0–29.9, ≥ 30 kg/m^2), maternal comorbidity (i.e. hypertension, pre-eclampsia, diabetes mellitus [insulin and non-insulin dependent], and heart disease), maternal infection during the first trimester of pregnancy, parity (0, 1, ≥ 2), month and year of conception. We identified maternal infection by linking the birth registry with the DAD and the National Ambulatory Care Reporting System (NACRS), which are two health administrative databases in Ontario that report hospital admissions and emergency room visits, respectively. We identified maternal viral infections from these databases based on a recent meta-analysis (Ye et al., 2019). We obtained information on pre-existing hypertension status among pregnant women by linking maternal information from the birth registry with the Ontario hypertension database, a validated registry of Ontario residents with diagnosed hypertension (Tu et al., 2007). We used the Ontario Diabetes Database, a validated registry of diabetics in Ontario, to identify pregnant women with and without diabetes before their pregnancy (Hux et al., 2002). Heart disease status was captured by linking maternal information with the DAD. The presence of preeclampsia was ascertained for a sub-sample of the whole cohort through routine measures of blood pressure and proteinuria after 20 weeks of gestation using established diagnostic criteria (Magee et al., 2008), but there is some level of missing information status for pre-eclampsia.

We also abstracted three contextual socioeconomic status (SES) variables (i.e. median family income, proportion of visible minority, and percentage of female aged 25–64 years who completed post-secondary education).

2.5. Statistical analysis

The associations between exposure to ambient air pollution during gestational weeks 2 to 8 and risk of CHDs were evaluated with random-effects logistic regression models. We assigned random-effects by neighborhoods (n = 140) and we assumed that any two neighborhoods were independent (Bai et al., 2018; Weichenthal et al., 2017). We also used random-effects in order to account for clustering within families (i.e. accounting for births to the same mother over time) (Lavigne et al., 2017). Weekly air pollution estimates were averaged across gestational weeks 2 to 8 of pregnancy to create a single measure of exposure (Stingone et al., 2017). The exposure-response associations were linear after preliminary analyses and therefore only models accounting for linearity were included here. The average effects over weeks 2 to 8 of pregnancy were reported as odds ratios (OR) and 95% confidence interval (CI) which corresponded to increases across the interquartile ranges (IQR) of UFPs, NO_2, $PM_{2.5}$ and O_3.

Potential confounders were evaluated in the multivariable models using covariates previously mentioned using a backward deletion approach (Rothman et al., 2008). This was done by adjusting for all potential confounders and then removing the covariate with the largest p-value one by one in a stepwise manner as long as the total proportional change in the odds ratio estimate compared with the fully adjusted model was < 10%. Covariates that were not found to be confounders, but increased the precision of the odds ratio estimates were kept in the final model.

To examine the robustness of our effect estimates, we conducted a sensitivity analysis excluding women with comorbidity (Auger et al., 2017). Statistical analyses were conducted using the R software (version 3.1.4). Ethics approval for this study was granted by the Research Ethics Boards of Health Canada and the Ottawa Health Science Network.

3. Results

A total of 158,743 singleton live births were identified from the birth registry between April 1st 2006 and March 31st 2012 (Table 1). Among these births, 1468 had a diagnosis of CHD. Compared with the overall cohort, cases of CHD had a smaller birth weight

Table 1
Selected demographic and socioeconomic characteristics of study participants.

Characteristics	Total cohort	Congenital heart defects
Maternal age, mean (SD)	31.1 (5.5)	31.4 (6.1)
Infant sex, n (%)		
Female	77,034 (48.5)	638 (43.5)
Male	81,709 (51.5)	830 (56.5)
Parity, n (%)		
0	91,161 (57.4)	847 (57.7)
1	48,117 (30.3)	410 (27.9)
≥ 2	19,465 (12.3)	211 (14.4)
Maternal smoking during pregnancy, n (%)		
Yes	6877 (4.3)	86 (5.9)
No	135,704 (85.5)	1138 (77.5)
Unknown	16,162 (10.2)	244 (16.6)
Gestational age, mean (SD)	38.8 (1.8)	34.7 (5.4)
Birth weight, mean (SD)	3319.9 (541.0)	2534.5 (1153.1)
Maternal diabetes, n (%)		
Yes	3174 (2.0)	76 (5.2)
No	155,569 (98.0)	1392 (94.8)
Maternal infection, n (%)		
Yes	1029 (0.6)	14 (1.0)
No	157,714 (99.4)	1454 (99.0)
Maternal preeclampsia, n (%)		
Yes	581 (0.4)	34 (2.3)
No	41,973 (26.4)	567 (38.6)
Unknown	116,189 (73.2)	867 (59.1)
Median family income, n (%)		
Quintile 1	31,457 (19.8)	316 (21.5)
Quintile 2	31,620 (19.9)	324 (22.1)
Quintile 3	31,590 (19.9)	319 (21.7)
Quintile 4	31,555 (19.9)	242 (16.5)
Quintile 5	31,549 (19.9)	258 (17.6)
Missing	972 (0.6)	9 (0.6)
Percent of females completed postsecondary education, n (%)		
Quintile 1	31,470 (19.8)	330 (22.5)
Quintile 2	31,581 (19.9)	305 (20.8)
Quintile 3	31,579 (19.9)	289 (19.7)
Quintile 4	31,344 (19.7)	287 (19.6)
Quintile 5	31,797 (20.0)	248 (16.9)
Missing	972 (0.6)	9 (0.6)
Percent visible minority, n (%)		
Quintile 1	31,509 (19.8)	244 (16.6)
Quintile 2	31,580 (19.9)	269 (18.3)
Quintile 3	31,482 (19.8)	311 (21.2)
Quintile 4	31,568 (19.9)	304 (20.7)
Quintile 5	31,559 (19.9)	331 (22.5)
Missing	1045 (0.7)	9 (0.6)
Overall	158,743	1468 (0.9)

SD, standard deviation;

(2534.5 ± 1153.1 vs. 3319.9 ± 541.0 g), a shorter gestational length (34.7 ± 5.4 vs. 38.8 ± 1.8 weeks), were more often males (56.5% vs. 51.5%), were more often born to mothers who smoked during pregnancy (5.9% vs. 4.3%), mothers with a history of diabetes (5.2% vs. 2.0%) and mothers with a diagnosis of preeclampsia (2.3% vs. 0.4%). Those with a diagnosis of CHD were also more likely to be in the lower quintiles of family income and maternal education and in the upper quintile of neighbourhood percent of visible minorities.

During weeks 2 to 8 of pregnancy, the mean concentration of exposure to UFPs was 28,953 count/cm^3 (Table 2). The IQRs for UFPs, $PM_{2.5}$, NO_2 and O_3 over the exposure period of interest were 10,864 count/cm^3, 2.4 μg/m^3, 7.4 ppb and 9.7 ppb, respectively. There were weak correlations between UFPs and $PM_{2.5}$ (Pearson correlation coefficient, $r = 0.06$) as well as between UFPs and NO_2 ($r = 0.01$) (Supplementary Table E1). A negative weak correlation was observed between UFPs and O_3 ($r = -0.11$). These weak correlations between UFPs and other pollutants are consistent with previous studies conducted in Montreal and Toronto in Canada (Weichenthal et al., 2014; Weichenthal et al., 2017). Average weekly concentrations of UFPs based on the temporal adjustment are shown in Supplementary Fig. E1. Weekly concentrations during the cold season were characterized by higher levels than weekly concentrations during the warm season, which is consistent with a recent study evaluating seasonal variability in UFPs in Toronto (de Jesus et al., 2019).

Table 3 presents the associations between each pollutant (i.e. UFPs, $PM_{2.5}$, NO_2 and O_3) and the odds of overall CHDs, ventricular septal defect and atrial septal defect. All models were adjusted for maternal age at delivery, infant sex, parity, maternal smoking status during pregnancy, gestational age, birth weight, maternal diabetes, maternal preeclampsia, three neighbourhood-level socioeconomic status (SES) variables, random-effects for neighborhoods in the city of Toronto, and random-effects for clustering within families. Maternal infection status as well as other comorbidities (i.e. heart disease and hypertension) were not found to be confounders in our models. UFPs exposure during weeks 2 to 8 of pregnancy were not associated with the overall odds of CHDs [OR = 1.02; 95% CI: 0.96–1.08 for a 10,864 count/cm^3 (IQR) increase]. However, UFP concentrations were positively associated with ventricular septal defects (OR = 1.09; 95% CI: 1.01–1.18). No other associations between UFPs exposure and CHD subtypes were observed in single pollutant models (Table 3 & Supplemental Tables E2). In the multi-pollutant models adjusted for $PM_{2.5}$, NO_2 and O_3, exposure to UFPs remained positively associated with ventricular septal defect (OR = 1.13; 95% CI: 1.03–1.33) (Table 4).

In analyses investigating effects of other pollutants, exposure to $PM_{2.5}$ was associated with ventricular septal defects (OR = 1.18; 95% CI: 1:01–1.38) (Table 3), but effects did not remain significant after adjustment for the other pollutants (OR = 1.01; 95% CI: 0.81–1.26) (Supplemental Table E4). No statistically significant associations were found for NO_2 on any CHD subtypes (Table 3 and Supplemental Tables E2 & E5). We found associations between O_3 and atrial septal defect as well as atrioventricular defect (Table 3 and Supplemental Table E2). However, these associations were not statistically significant when additionally adjusting for the other pollutants (Supplemental Table E6).

In the sensitivity analyses, we did not find differences in effect estimates when analyzing only the cohort of women without any of the investigated comorbidities (results not shown).

4. Discussion

In this study, we evaluated associations between exposure to UFPs during weeks 2 to 8 of pregnancy and risk of CHDs. Our findings indicate that UFP exposures may be associated with an increased risk of ventricular septal defects after adjusting for other air pollutants. We did not find evidence for an association between other air pollutants and any of the congenital anomaly groups studied.

Previous studies have not investigated the association between exposure to UFPs and risk of CHDs. However, several studies have focused on the effects of $PM_{2.5}$ and risk of CHDs, with inconsistent results reported. In a recent case-control study conducted in Taiwan, authors found associations between exposure to $PM_{2.5}$ during weeks 3 to 8 of

Table 2
Descriptive statistics of exposure to ambient air pollutants.

Air pollutants	Mean (SD)	Median	IQR	Range
UFPs (count/cm^3)	28,953 (9150)	26,789	10,864	77,698
$PM_{2.5}$ (μg/m^3)	9.2 (1.8)	9.1	2.4	18.5
NO_2 (ppb)	16.1 (5.7)	15.3	7.4	54.6
O_3 (ppb)	23.8 (6.1)	24.2	10.8	31.9

SD, standard deviation; IQR, inter-quartile range.

Table 3
Odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between UFPs (per IQR), $PM_{2.5}$ (per IQR), NO_2 (per IQR), O_3 (per IQR) and risk of congenital heart defects.[a,b]

Congenital Heart Defects	Obs. cases	UFPs	$PM_{2.5}$	NO_2	O_3
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall Congenital Heart Defects	1468	1.02 (0.96–1.08)	1.05 (0.97–1.13)	1.02 (0.94–1.10)	0.97 (0.87–1.08)
Ventricular septal defect	326	1.09 (1.01–1.18)	1.18 (1.01–1.38)	1.01 (0.85–1.20)	1.17 (0.92–1.49)
Atrial septal defect	581	0.97 (0.87–1.07)	1.10 (0.98–1.23)	1.05 (0.93–1.19)	1.22 (1.02–1.45)

[a] Odds ratio correspond to increases across the interquartile ranges (IQRs) of UFPs (10,864 count/cm^3), $PM_{2.5}$ (2.4 μg/m^3), NO_2 (7.4 ppb), and O_3 (10.8 ppb).
[b] Model adjusted for maternal age at delivery, infant sex, parity, maternal smoking status during pregnancy, gestational age, birth weight, maternal diabetes, maternal preeclampsia, three neighbourhood-level socioeconomic status (SES) variables, random-effects for neighbourhood in the city of Toronto, and random effects for clustering within families.

pregnancy and overall CHDs, atrial septal defect, endocardial cushion defect and pulmonary artery and valve stenosis (Huang et al., 2019). In addition, results based on 105,988 births in a study in Wuhan (China) found that $PM_{2.5}$ increased risk of overall CHDs, particularly ventricular septal defect during weeks 7 to 10 of pregnancy (odds ratios ranging from 1.11 to 1.17) (Zhang et al., 2016a). In a study conducted in California, $PM_{2.5}$ during the first two months of pregnancy was found to be associated with risk of transposition of the great arteries, but inversely associated with perimembranous ventricular septal defect and secundum atrial septal defect (Padula et al., 2013). Stingone et al. (2014) conducted a case-control study in nine states in the United-States and found that $PM_{2.5}$ exposure during weeks 2–8 of pregnancy was associated with hypoplastic left heart syndrome, but negatively associated with atrial septal defect (Stingone et al., 2014). In Barcelona, exposure to $PM_{2.5}$ during weeks 3–8 of pregnancy was inversely associated with ventricular septal defect, but not with overall CHD or other CHD subtypes (Schembari et al., 2014). In our study, we found an association between $PM_{2.5}$ and ventricular septal defects, but the association became not statistically significant when adjusting for other air pollutants.

The inconsistency in results previously reported for effects of $PM_{2.5}$ could also be related to the fact that smaller particles are driving the risk being observed. In our study, we report for the first time associations between UFPs and ventricular septal defect after adjustment for other air pollutants. Little is known regarding the impacts of UFPs and particles during the gestational period on cardiac fetal development. However, a recent review paper reported that maternal nanoparticles/ultrafine particles exposure in pregnant mice induce morphological malformations (Teng et al., 2016). In particular, it is hypothesized that ultrafine particles could induce malformations through oxidative stress (Jin et al., 2015; Ornoy, 2007), placental inflammation (Yue et al., 2019), compromised transplacental ability (Balansky et al., 2013) and altered gene expression or epigenetics (Bollati et al., 2010).

In this study, we did not find that exposure to NO_2 was associated with any CHD subtypes. Exposure to NO during pregnancy was previously found to increase the risk of ventricular septal defect and cardiac septal malformations (Dadvand et al., 2011a; Dadvand et al., 2011b). In a study conducted in Barcelona, exposure to NO_2 during weeks 3 to 8 of pregnancy was associated with coarctation of the aorta (Schembari et al., 2014). The fact that we did not observe similar findings to previous studies can be attributed to different exposure assessment methods and differences in local air pollution emission sources.

Our findings also showed that O_3 was potentially associated with atrial septal defect as well as atrioventricular defect, but the associations did not remain statistically significant when adjusting for other pollutants. In a study conducted in Wuhan, China, authors found associations between exposure to O_3 and overall CHDs, ventricular septal defect and tetralogy of Fallot with effect estimates remaining statistically significant in multi-pollutant models (Zhang et al., 2016a). In another study conducted in Taiwan, each 10 ppb increases in O_3 exposure during the first 3 gestational months were associated with the risks of ventricular septal defects, atrial septal defects, and patent ductus arteriosus (Hwang et al., 2015). However, effect estimates were not adjusted for other pollutants. Further studies are required regarding the impact of O_3 on risk of CHD when investigating these impacts in multi-pollutant models.

It is important to acknowledge several limitations of this study. First, we evaluated multiple air pollution measures on the risk of CHDs and CHD subtypes which might have given rise to chance associations. Our exposure estimates for UFPs and NO_2 for the time period under study were assigned using LUR models based on data collected from short-term monitoring campaigns using a temporal scaling adjustment in order to capture different periods of exposure. We were therefore unable to obtain spatial-temporal ground estimates measured across the City of Toronto due to technological challenges and high costs. Also, our monitoring campaign for developing models for UFPs was conducted toward the end of the study time period. However, we applied previously published methods in order to capture as accurately as possible temporal changes in UFPs and NO_2 (Bechle et al., 2015;

Table 4
Odds ratios (OR) and 95% confidence intervals (95% CI) for the associations between UFPs (per IQR) and risk of congenital heart defects with additional adjustment for $PM_{2.5}$, NO_2 and O_3.[a,b]

Congenital Heart Defects	UFPs + $PM_{2.5}$	UFPs + NO_2	UFPs + O_3	UFPs + $PM_{2.5}$ + NO_2 + O_3
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Overall Congenital Heart Defects	1.02 (0.90–1.15)	0.99 (0.91–1.09)	1.04 (0.97–1.11)	1.03 (0.92–1.14)
Ventricular septal defect	1.18 (0.89–1.55)	1.05 (0.86–1.25)	1.27 (1.01–1.62)	1.13 (1.03–1.33)
Atrial septal defect	1.24 (1.02–1.52)	0.89 (0.76–1.03)	0.99 (0.89–1.12)	0.89 (0.74–1.06)

[a] Odds ratio correspond to increases across the interquartile range (IQR) of UFPs (10,864 count/cm^3).
[b] Model adjusted for maternal age at delivery, infant sex, parity, maternal smoking status during pregnancy, gestational age, birth weight, maternal diabetes, maternal preeclampsia, three neighbourhood-level socioeconomic status (SES) variables, random-effects for neighbourhood in the city of Toronto, and random effects for clustering within families.

Weichenthal et al., 2016a) which were applied in a recent publication of our study group (Lavigne et al., 2019). However, our UFP exposure model could be impacted by broad changes in emissions over time and could be impacted by local changes in infrastructure that could influence the movement of traffic sources through space. This likely resulted in exposure misclassification, but a systematic difference in the magnitude of exposure error by CHD case status seems unlikely and the overall impact of exposure measurement error was likely a bias toward the null. In addition, since outdoor UFP concentrations have likely decreased over time, our data may not be appropriate in identifying absolute threshold values for UFP impacts on CHDs if overall exposure levels were elevated toward the beginning of the follow-up period. We also need to acknowledge that there may be potential residual confounding. For example, no individual-level information was available for income, education, ethnicity and use of folic-acid supplements and medications during pregnancy (Schembari et al., 2014). However, we controlled for some neighbourhood-level SES factors, which may have partially accounted for these missing variables. We were also not able to provide information on CHD cases that were identified from different sources (i.e. ultrasound exams during pregnancy and postnatal exams) as this information was not available from health administrative data. In addition, there may be some level of uncertainty in estimating conception dates which likely affected our capacity in identifying the critical window under study. However, this level of error is likely the same for all participants and potentially resulted in an underestimation of risk estimates.

Some of the strengths of this study include the air pollution exposure estimates that captured both spatial and temporal variation, the large sample size and several important confounders included in the analyses. We also identified CHDs based on hospital discharge records at birth which have been previously used in Canada and have shown high sensitivity and specificity (Auger et al., 2017). The risk of selection bias was likely reduced due to the population-based approach we used. This is also the first study, to our knowledge, to examine the effects of prenatal exposure to UFPs on the risk of CHDs.

5. Conclusion

In this study, we found that exposure to UFPs during weeks 2 to 8 of pregnancy was associated with increased odds of ventricular septal defect independent of other air pollutants including $PM_{2.5}$, NO_2 and O_3. Further research is needed on the effects of UFPs on cardiac foetal development.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.104953.

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