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Maternal exposure to ambient air pollution and congenital heart defects in China

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ABSTRACT

Background: Evidence of maternal exposure to ambient air pollution on congenital heart defects (CHD) has been mixed and are still relatively limited in developing countries. We aimed to investigate the association between maternal exposure to air pollution and CHD in China.

Method: This longitudinal, population-based, case-control study consecutively recruited fetuses with CHD and healthy volunteers from 21 cities, Southern China, between January 2006 and December 2016. Residential address at delivery was linked to random forests models to estimate maternal exposure to particulate matter with an aerodynamic diameter of $\leq$ 1 μm (PM_1), $\leq$2.5 μm, and $\leq$10 μm as well as nitrogen dioxides, in three trimesters. The CHD cases were evaluated by obstetrician, pediatrician, or cardiologist, and confirmed by cardia ultrasound. The CHD subtypes were coded using the International Classification Diseases. Adjusted logistic regression models were used to assess the associations between air pollutants and CHD and its subtypes.

Results: A total of 7055 isolated CHD and 6423 controls were included in the current analysis. Maternal air pollution exposures were consistently higher among cases than those among controls. Logistic regression analyses showed that maternal exposure to all air pollutants during the first trimester was associated with an

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increased odds of CHD (e.g., an interquartile range [13.3 μg/m^3] increase in PM_1 was associated with 1.09-fold ([95% confidence interval, 1.01–1.18]) greater odds of CHD). No significant associations were observed for maternal air pollution exposures during the second trimester and the third trimester. The pattern of the associations between air pollutants and different CHD subtypes was mixed.

Conclusions: Maternal exposure to greater levels of air pollutants during the pregnancy, especially the first trimester, is associated with higher odds of CHD in offspring. Further longitudinal well-designed studies are warranted to confirm our findings.

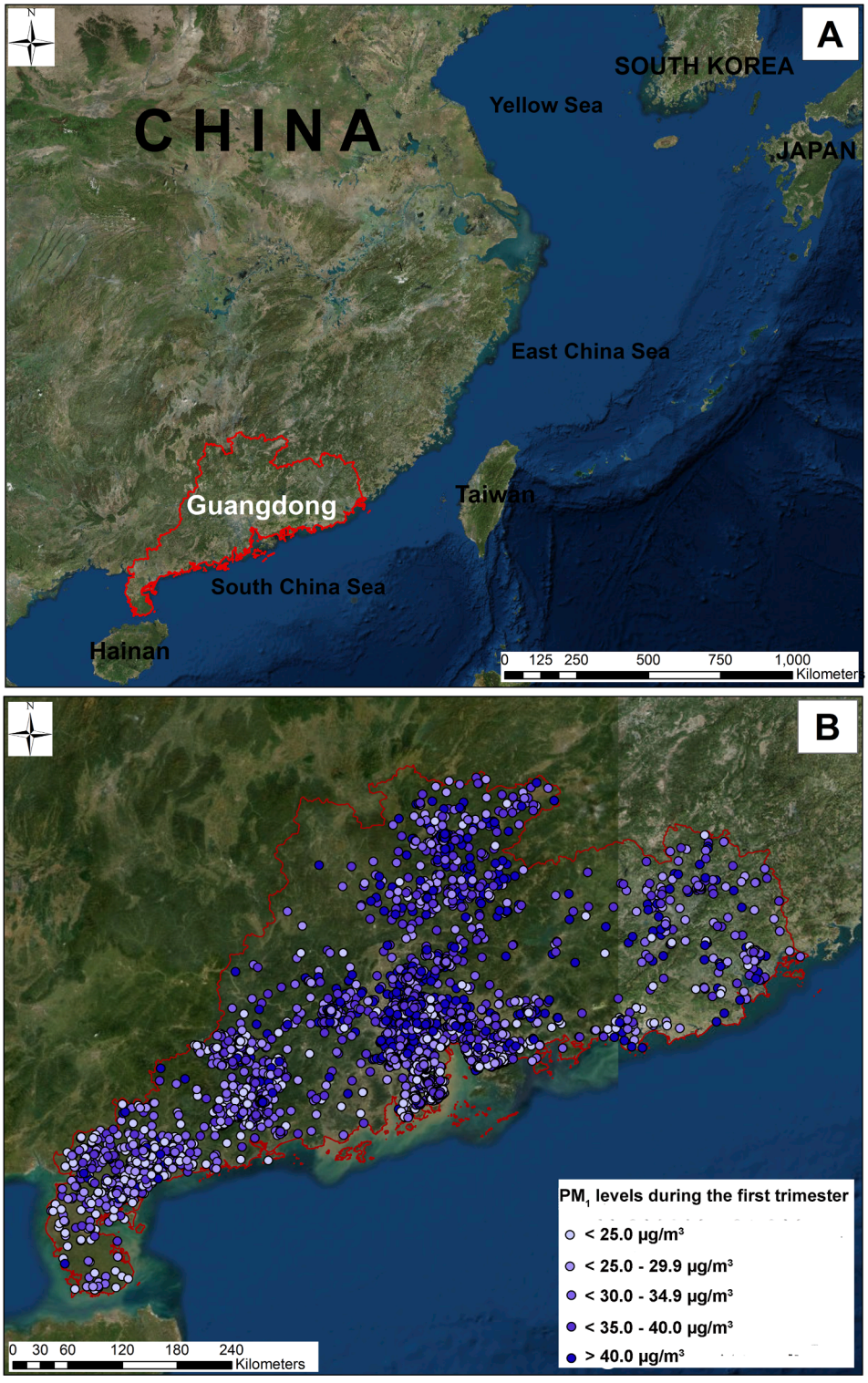

Fig. 1. Location of the study area on the map of China (Panel A) as well as locations of the study participants in Guangdong province (Panel B).

1. Introduction

Congenital heart defects (CHD) is a leading cause of infant morbidity and mortality (van der Linde et al., 2011). Globally, the prevalence of CHD has reached 9.4 per thousand, with Asia having the highest prevalence (Liu et al., 2019). In China, a national survey between 2010 and 2012 showed that the overall CHD prevalence was 9.0 per thousand (Zhao et al., 2019). The etiology of CHD is complicated with both genetic and environmental factors involved (Blue et al., 2012).

Ambient air pollution is one of the leading risk factors for many disorders and has become a global environmental problem. Mechanistically, maternal exposure to air pollution during pregnancy may be involved in CHD by increasing placental oxidative stress and inflammation (Ornoy, 2007; Qi et al., 2014), inducing epigenetic changes (Avissar-Whiting et al., 2010; Bollati et al. 2010), and comprising transplacental ability (Balansky et al., 2013). An increasing number of epidemiological studies have investigated the association between maternal exposure to ambient air pollution and CHD, but the results are inconsistent (these studies are listed in Table S1 and also summarized in Hu et al. (2020)). In addition, while most of the prior studies were conducted in developed nations with lower air pollution levels (Agay-Shay et al., 2013; Farhi et al., 2014; Vinceti et al., 2016; Padula et al., 2013; Stingone et al., 2014; and also see Table S1), a few of them have also been conducted in Chinese population where air pollution was severe (Ren et al., 2018; Liu et al., 2017; and also see Table S1). Still, the results of those Chinese studies were inconsistent, and evidence for each air pollutant was limited. Moreover, the exposure assessment in most of the prior studies were based on assigning the air pollution data from a single or limited number of air monitoring stations (Agay-Shay et al., 2013; Farhi et al., 2014; Padula et al., 2013; Stingone et al., 2014; Ren et al., 2018; Liu et al., 2017; and also see Table S1), which may have caused exposure misclassification.

In the present study, we aimed to assess the relationships between maternal exposure to air pollution and CHD in offspring among a southern Chinese population by analyzing the data from the Guangdong Registry of Congenital Heart Disease (GRCHD), a large longitudinal case-control study.

2. Methods

2.1. Study area

This case-control study was conducted in Guangdong province, southern China (Fig. 1). We identified CHD cases using data from the GRCHD, which is an ongoing populated-based CHD surveillance system in Guangdong province since 2004. As air pollution data were not available before 2005, we only used data after January 2006. The GRCHD includes 39 collaborative hospitals, covering 21 major cities and their surrounding rural areas. All CHD cases were mandatorily reported by obstetricians, ultrasound physicians, and pediatricians to the GRCHD system. Controls were randomly selected among singleton newborns without any malformation, and were matched with cases by infant sex, date of conception, maternal residence, and delivery hospital. The study was approved by the Human Subjects Committees of Guangdong General hospital. All study participants gave informed consents.

3. Definitions of cases and controls

Cases were live-born infants, stillborn fetuses and late miscarriages over 17 weeks' gestation diagnosed with CHD. All deliveries were examined by an obstetrician, pediatrician, or pediatric cardiologist before discharge or within three days after birth. Two specially trained echocardiologists independently reviewed each of the echocardiograms of CHD cases. If necessary, a CHD case was further confirmed by computed tomography, cardiac catheterization, surgery, or autopsy. We initially recruited 10 660 CHD cases. Of these, we excluded 95 cases with syndromes caused by gene mutations or chromosomal aberrations (in order to exclude the effects of genetic factors (Boyd et al., 2011)), 642 non-singleton infants (who tend to have different etiology of CHD than singletons), 981 preterm infants with only patent ductus arteriosus (who would close spontaneously by 44 weeks postmenstrual age (Slaughter et al., 2019)), 455 infants aged over one year old (to minimize recall bias of self-reported pregnancy lifestyle factors), and 408 non-isolated CHD with extra-cardiac defects (to detect the specific effect of air pollution on isolated CHD). We further excluded 730 cases whose air pollution data could not be assigned and 594 cases whose information on delivery date was missing or apparently not correct. Finally, 7055 CHD cases were included into the current analysis (Fig. 2). All cases were classified using international classification of disease 10 codes, and an *a priori* decision was made to analyze the following common subgroups of anomalies: ventricular septal defect (VSD; Q21.001), atrial septal defect (ASD; Q21.102), d-transposition of the great arteries (TGA, Q20.302), tetralogy of Fallot (ToF, Q21.300), valvular pulmonaty stenosis (vPS, Q22.101), atrioventricular septal defect (AVSD, Q21.200), and double outlet right ventricle (DORV, Q20.101).

For Controls, a total of 7357 non-singleton deliveries were enrolled initially. We then excluded 439 infants aged over one year old (minimize recall bias of self-reported pregnancy lifestyle factors), 307 without exact delivery date or incorrect delivery date, and 188 that air pollution exposure cannot be assigned, giving a final sample of 6423 participants (Fig. 2).

4. Maternal air pollution exposure assessment

We estimated daily concentrations of $PM_{2.5}$, particles with diameter $\leq$ 1.0 μm (PM_1), $\leq$10 μm (PM_{10}), and nitrogen dioxide (NO_2) for mainland China by adopting a random forests model at a spatial resolution of 0.1 degree, using satellite remote sensing, land use, and meteorologic information (Chen et al., 2018a; 2018b). We geocoded the residential address of each woman at delivery and matched to the centroid of the nearest grid cell of predicted air pollutants. We then calculated the last menstrual period based on the date of birth and gestational age. Daily exposures were averaged over four exposure windows: the first trimester (1–13 weeks' gestation), the second trimester (14–26 weeks' gestation), the third trimester (27 weeks to delivery), and the entire pregnancy period. The first trimester is often considered as a critical window for a fetus to develop CHD (Opitz and Clark 2000), we thus focused on this trimester exposure in the main analysis.

4.1. Statistical analysis

We employed logistic regression models to examine the associations of air pollution exposure with CHD cases and different CHD subtypes. The odds ratios (ORs) and corresponding confidence intervals (CIs) were calculated for an interquartile range (IQR) increase in air pollutant concentrations. We selected confounders according to the methods suggested by Jager et al. (2008), in which a confounder should meet the following three criteria: (1) it should be a risk factor for CHD; (2) it must be a "cause" of the air pollution exposure and unequally distributed across groups with different air pollution levels; and (3) it must not be an "effect" of air pollution exposure, nor be an intermediate factor in the causal pathway between air pollution and CHD. We used a multilevel structured questionnaire in combination with a pregnancy calendar, which is helpful for mothers to recall the major milestones of pregnancy, to collect data on potential confounders. Then, we developed a directed acyclic graph (DAG) to select a minimally sufficient set of adjustments (Greenland et al., 1999). According to the DAG (Figure S1 in the supplement), the following confounders were adjusted in the main models: maternal age of delivery (years), ethnicity (Han or others), highest level of maternal education (illiteracy/primary/middle school, completion of

high school, and college or above), maternal occupation (manual worker, farmer, house keeper, and others), household income (≥3001, 2001–3000, and <2000 Yuan per year), maternal smoking during pregnancy (yes or no), partner smoking during pregnancy (yes or no), season of conception (spring, summer, autumn, and winter), residential area (rural or urban), maternal exposures to metals or pesticide or organic solvents (yes or no), and birth year. We performed several sensitivity analyses. First, we employed pollutant-residuals models to explore if an individual pollutant showed a significant association with CHD. Due to high correlation between pollutants, we regressed the highly correlated pollutants each other and the residuals were then incorporated into the models for associations of air pollutants with CHD (Flexeder et al., 2017). Second, we repeated the association between CHD and air pollution during the second and the third trimesters. Similarly, due to significant correlations between air pollutant concentrations across the trimesters, we regressed them against each other and then included the residuals from the regression analyses into the models for air pollutant concentrations at the second and third trimesters with CHD. Third, we estimated the air pollution-CHD association by excluding participants whose house was decorated during last six months, those who experienced viral infection during the first trimester, or those who had gestational hypertension or diabetes. We also repeated the analyses by additional adjustment for fetal sex, maternal alcohol consumption, parity, gravidity, folate intake during pregnancy, abnormal birth history (e.g., stillbirth or pregnancy loss), intake of abortion prevention agents, and hospital. The above factors cannot be selected as confounders according to the criteria suggested by Jager et al. (2008), but may affect the odds of CHD, thus we performed these sensitivity analyses to assess their potential impact. Finally, we categorized air pollution concentration into quartiles to explore linearity of the associations.

We also tested the effect modification effects by maternal age (<35 years versus ≥35 years), highest level of parental education level completed (college or above versus middle school or lower), household registration (rural versus urban), neonate's sex (male versus female), and season of conception (spring or winter versus summer or fall). Finally, we explored the associations between air pollutants and different CHD subtypes.

All statistical analyses were performed on SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). A two-tailed *P* value less than 0.05 was considered statistically significant.

5. Results

In total, 7055 isolated CHD and 6423 controls were included (Table 1). Compared with deliveries without CHD, infants with CHD were more likely to be male (60.3% vs 57.3%), to live in rural area (40.6% vs 37.5%), to be born to a family with a lower household income (61.7% vs 55.9%), to have had a father smoking after conception (21.8% vs 14.7%), to have had a mother with lower education level (9.6% vs 6.0%), as well as who had smoked during pregnancy (1.4% vs 0.4%) or had drunk alcohol during pregnancy (0.8% vs 0.3%), and was a manual worker (11.5% vs 7.3%).

Maternal air pollutants levels in cases were significantly higher than those in controls (Table 2). For example, mean (SD) values of PM_1, $PM_{2.5}$, PM_{10}, and NO_2 in cases and controls during the first trimester were 35.20 (8.62) and 34.78 (8.64), 43.83 (10.80) and 43.21 (10.78), 68.18 (14.87) and 67.22 (14.85), and 30.61 (11.79) and 29.89 (11.39) $\mu g/m^3$, respectively (Table 2). Correlation between the air pollutants was high (r_s ranged from 0.73 to 0.99) (Table S2 in the supplement).

Air pollution exposure during the first trimester was associated with greater odds of CHD both in crude and adjusted models (Table 3 and Table S3 in the supplement). More specifically, in the adjusted models, an IQR increase in PM_1 (13.3 $\mu g/m^3$), $PM_{2.5}$ (16.1 $\mu g/m^3$), PM_{10} (22.3 $\mu g/m^3$), and NO_2 (17.2 $\mu g/m^3$) was associated with a 1.09- (95% CI, 1.01–1.18), 1.10- (95% CI, 1.03–1.19), 1.11- (95% CI, 1.04–1.20), and 1.13- fold (95% CI, 1.06–1.20) increased odds of CHD, respectively. Air pollution during the second and third trimesters was also associated with higher odds of CHD, although most of the associations did not reach statistical significance (Table 3).

The above significant associations were confirmed in sensitivity analyses adopting pollutant-residuals models (Table S4 in the supplement). We excluded several specific participants and found the estimates were not substantially changed (Table S5 in the supplement). We repeated analyses by individually adjusting the main model for some potential risk factors of CHD, and found the estimates were consistent with those

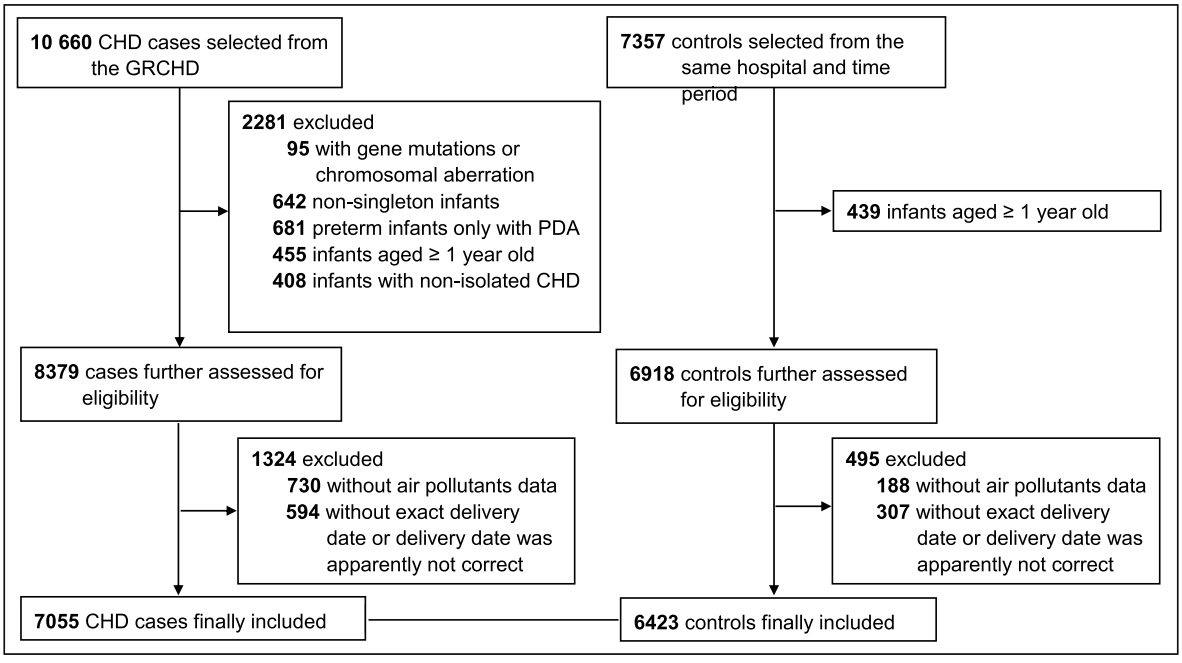

Fig. 2. Flow chart of study participant selection. Note: CHD, congenital heart defects; GRCHD, Guangdong Registry of Congenital Heart Disease; PDA, patent ductus arteriosus.

Table 1
Maternal and fetal characteristics of congenital heart defects cases and controls.

Characteristics	N (%)		P-Value
	Cases (n = 7055)	Controls (n = 6423)	
Maternal age, y			<0.001
<35	6383 (90.5)	5961 (92.8)	
≥35	672 (9.5)	462 (7.2)	
Maternal Ethnicity			0.001
Han	6953 (98.6)	6371 (99.2)	
Others	102 (1.4)	52 (0.8)	
Maternal educational level			<0.001
College or above	1160 (16.4)	1295 (20.2)	
Completion of high school	5216 (73.9)	4741 (73.8)	
Illiteracy /Primary / Middle School	679 (9.6)	387 (6.0)	
Maternal occupation			<0.001
Manual worker	812 (11.5)	469 (7.3)	
Farmer	893 (12.7)	853 (13.3)	
House keeper	482 (6.8)	408 (6.4)	
Scientific and technological personnel	426 (6.0)	454 (7.1)	
Service staff	1647 (23.3)	1558 (24.3)	
Laid-off employees	2054 (29.1)	1962 (30.6)	
Others	741 (10.5)	719 (11.2)	
Household income, yuan per month			
≥3001	2699 (38.3)	2831 (44.1)	<0.001
2001–3000	1588 (22.5)	1586 (24.7)	
<2000	2768 (39.2)	2006 (31.2)	
Maternal organic solvents, pesticide, or metal exposure after conception			<0.001
Yes	229 (3.3)	85 (1.3)	
No	6826 (96.7)	6338 (98.7)	
Maternal smoking after conception			<0.001
Yes	98 (1.4)	23 (0.4)	
No	6957 (98.6)	6400 (99.6)	
Partner smoking after conception			<0.001
Yes	1536 (21.8)	942 (14.7)	
No	5519 (78.2)	5481 (85.3)	
Maternal drinking after conception			<0.001
Yes	53 (0.8)	19 (0.3)	
No	7002 (99.2)	6404 (99.7)	
Household registration			<0.001
Urban	4191 (59.4)	4014 (62.5)	
Rural	2864 (40.6)	2409 (37.5)	
Neonate's sex			<0.001
Male	4251 (60.3)	3683 (57.3)	
Female	2773 (39.3)	2739 (42.6)	
Unclear	31 (0.4)	1 (0.02)	
Season of conception			0.94
Spring	1817 (25.8)	1670 (26.0)	
Summer	1635 (23.2)	1503 (23.4)	
Autumn	1682 (23.8)	1531 (23.8)	
Winter	1921 (27.2)	1719 (26.8)	
Birth year			
2004–2010	2284 (32.4)	1686 (26.3)	
2010–2016	4771 (67.6)	4737 (73.7)	

from the main analysis (Table S6 in the supplement). We also categorized air pollutants into quartiles and found that estimated ORs gradually increased with greater quartiles of air pollutants concentrations (Table S7 in the supplement).

In stratified analyses, the associations between air pollution and CHD seemed to be stronger in male cases, born to a rural area, born in warmer seasons, and born to a mother with greater gestational age or having lower education level than in their counterparts. However, most of the differences was not statistically significant, with the exception of NO_2 with maternal education level and neonate's sex (Table S8 in the supplement).

Table 2
Mean (SD) of air pollutants exposures, by cases and controls.

Pollutant	Cases mean (SD), μg/m³	Controls mean (SD), μg/m³	p-Value
Overall pregnancy			
PM_1	34.76 (5.30)	34.44 (5.23)	<0.001
$PM_{2.5}$	43.31 (6.84)	42.84 (6.73)	<0.001
PM_{10}	67.48 (9.95)	66.75 (9.81)	<0.001
NO_2	30.22 (9.96)	29.60 (9.55)	<0.001
First trimester			
PM_1	35.20 (8.62)	34.78 (8.64)	0.005
$PM_{2.5}$	43.83 (10.80)	43.21 (10.78)	0.001
PM_{10}	68.18 (14.87)	67.22 (14.85)	<0.001
NO_2	30.61 (11.79)	29.89 (11.39)	<0.001
Second trimester			
PM_1	34.45 (8.74)	34.19 (8.84)	0.09
$PM_{2.5}$	42.96 (10.93)	42.57 (11.01)	0.04
PM_{10}	66.90 (15.02)	66.38 (15.10)	0.02
NO_2	30.02 (11.82)	29.46 (11.46)	0.005
Third trimester			
PM_1	34.63 (8.30)	34.37 (8.29)	0.08
$PM_{2.5}$	43.14 (10.40)	42.76 (10.28)	0.03
PM_{10}	67.27 (14.32)	66.64 (14.19)	0.01
NO_2	30.01 (11.54)	29.45 (11.10)	0.004

Note: NO_2, nitrogen dioxide; PM_1, particle with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particle with aerodynamic diameter ≤ 10 μm; SD, standard deviation.

When we grouped CHD cases into seven different subtypes, we found that the pattern of the association between air pollution and CHD subtypes were mixed (Table 4). While significant and positive associations were found for TGA and DORV, inverse associations were found for ASD, and no associations were detected for VSD, ToF, vPS, and AVSD.

6. Discussion

In this study, we estimated the association between maternal exposure to four air pollutants during pregnancy and the odds of CHD and its subtypes in off springs. In particular, we assessed PM_1, which was not previously studied in this field. We found that exposure to PM_1, $PM_{2.5}$, PM_{10}, and NO_2 during pregnancy, especially the first trimester, was consistently associated with greater odds of pooled CHD cases, and several sensitivity analyses demonstrated that the above associations were robust. The pattern of the associations between air pollution and different CHD subtypes was mixed.

In a systematic Medline literature search, we are aware of 14 studies evaluating the association of maternal exposure to air pollution with pooled CHD cases (these studies are summarized in Table S1 in the supplement), of which 10 studies reported positive association, three studies reported null association, and one study reported inverse association. More specifically, two birth cohorts in Israel (Agay-Shay et al., 2013; Farhi et al., 2014) and China (Ren et al., 2018) as well as one case-control study in China (Liu et al., 2017) observed that maternal exposure to PM_{10} during the first trimester was associated with increased odds of combined CHD cases, which is consistent with our current findings. However, several studies found no significant association (Vinceti et al., 2016; Zhang et al., 2016). Again, in line with our results, two cohorts in the United Sates (Tanner et al., 2015) and China (Zhang et al., 2016) as well as one case-control study in China (Huang et al., 2019) showed that maternal $PM_{2.5}$ exposure during the first trimester was associated with increased odds of combined CHD. However, the remaining studies observed null association between them. Similar mixed associations were also reported for the studies concerning NO_2 exposure and pooled CHD cases (Table S1 in the supplement). Despite this, the above comparisons of our findings with the published studies should be interpreted with great caution, because these studies are highly heterogeneous in CHD definitions, air pollutants assessments, air pollutants background levels, sources, and constituents, study participants' characteristics, and

Table 3
Associations between per IQR[a] increase in air pollutants and congenital heart defects in three trimesters (single-pollutant model).

	First trimester		Second trimester		Third trimester	
Air pollutants	OR (95% CI)[b]	*p*-Value	OR (95% CI)[c]	*p*-Value	OR (95% CI)[d]	*p*-Value
PM_1	1.09 (1.01, 1.18)	0.03	1.03 (0.94, 1.12)	0.51	1.06 (0.97, 1.15)	0.20
$PM_{2.5}$	1.10 (1.03, 1.19)	0.01	1.04 (0.96, 1.13)	0.36	1.07 (0.99, 1.15)	0.11
PM_{10}	1.11 (1.04, 1.20)	0.003	1.04 (0.97, 1.13)	0.28	1.08(1.00, 1.16)	0.06
NO_2	1.13 (1.06, 1.20)	<0.001	1.09 (1.02, 1.16)	0.01	1.09 (1.02, 1.17)	0.01

Note: CI, confidence interval; IQR, interquartile range; NO_2, nitrogen dioxide; OR, odds ratio; PM_1, particle with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particle with aerodynamic diameter ≤ 10 μm.

[a] IQR for the first trimester: PM_1, 13.3 μg/m^3; $PM_{2.5}$, 16.1 μg/m^3; PM_{10}, 22.3 μg/m^3; NO_2, 17.2 μg/m^3. IQR for the second trimester: PM_1, 14.1 μg/m^3; $PM_{2.5}$, 17.0 μg/m^3; PM_{10}, 23.2 μg/m^3, NO_2, 17.0 μg/m^3. IQR for the third trimester: PM_1, 12.8 μg/m^3; $PM_{2.5}$, 15.2 μg/m^3; PM_{10}, 21.1 μg/m^3; NO_2, 16.8 μg/m^3.

[b] Adjusted for maternal age, ethnicity, education, occupation, household income, maternal smoking during pregnancy, partner smoking during pregnancy, season of pregnancy, residential area, exposures to metals or pesticide or organic solvents, and birth year.

[c] Adjusted for maternal age, ethnicity, education, occupation, household income, maternal smoking during pregnancy, partner smoking during pregnancy, season of pregnancy, residential area, exposures to metals or pesticide or organic solvents, birth year, and residuals from regression models of air pollutants levels during the second trimester with those during the first trimester.

[d] Adjusted for maternal age, ethnicity, education, occupation, household income, maternal smoking during pregnancy, partner smoking during pregnancy, season of pregnancy, residential area, exposures to metals or pesticides or organic solvents, birth year, and residuals from regression models of air pollutants levels during the third trimester with those during the second and the first trimesters.

Table 4
Associations between air pollutants in the first trimester (per IQR increase[a]) and congenital heart defects subtypes (single-pollutant model).

		PM_1		$PM_{2.5}$		PM_{10}		NO_2	
Subtype	Case number	OR (95% CI)[b]	*p*-Value	OR (95% CI)[b]	*p*-Value	OR (95% CI)[b]	*p*-Value	OR (95% CI)[b]	*p*-Value
VSD	2131	0.94 (0.85, 1.05)	0.27	0.98 (0.89, 1.09)	0.71	0.96 (0.87, 1.06)	0.42	1.06 (0.98, 1.16)	0.16
ASD	1475	0.85 (0.75, 0.96)	0.008	0.82 (0.73, 0.92)	0.001	0.83 (0.74, 0.93)	0.001	0.70 (0.63, 0.77)	<0.001
TGA	284	1.36 (1.03, 1.78)	0.03	1.32 (1.02, 1.70)	0.03	1.40 (1.09, 1.79)	0.008	1.67 (1.36, 2.05)	<0.001
ToF	209	1.12 (0.81, 1.54)	0.50	1.04 (0.77, 1.39)	0.82	1.08 (0.81, 1.44)	0.59	0.98 (0.76, 1.25)	0.85
vPS	171	0.83 (0.59, 1.16)	0.27	0.83 (0.60, 1.14)	0.58	0.84 (0.62, 1.15)	0.28	1.08 (0.82, 1.44)	0.57
AVSD	136	1.18 (0.80, 1.75)	0.41	1.19 (0.82, 1.72)	0.36	1.18 (0.82, 1.68)	0.38	1.25 (0.92, 1.70)	0.15
DORV	121	2.10 (1.35, 3.26)	0.001	2.14 (1.43, 3.22)	<0.001	2.12 (1.42, 3.15)	0.0002	2.01 (1.47, 2.75)	<0.001
Others	2528	1.25 (1.13, 1.38)	<0.001	1.25 (1.14, 1.38)	<0.001	1.27 (1.16, 1.39)	<0.001	1.25 (1.15, 1.35)	<0.001

Note: ASD, atrial septal defect; AVSD, atrioventricular septal defect; CI, confidence interval; DORV, double outlet right ventricle; NO_2, nitrogen dioxide; OR, odds ratio; PM_1, particle with aerodynamic diameter ≤ 1.0 μm; $PM_{2.5}$, particle with aerodynamic diameter ≤ 2.5 μm; PM_{10}, particle with aerodynamic diameter ≤ 10 μm; TGA, d-transposition of the great arteries; ToF, tetralogy of Fallot; vPS, valvular pulmonary stenosis; VSD, ventricular septal defect.

[a] IQR for the first trimester: PM_1, 13.3 μg/m^3; $PM_{2.5}$, 16.1 μg/m^3; PM_{10}, 22.3 μg/m^3; NO_2, 17.2 μg/m^3.

[b] Adjusted for maternal age, ethnicity, education, occupation, household income, maternal smoking during pregnancy, partner smoking during pregnancy, season of pregnancy, residential area, birth year, and exposures to metals or pesticide or organic solvents.

the adjustment sets. To the best of our knowledge, this is the first study to explore the teratogen effects of PM_1. We found that greater PM_1 exposure during the first trimester of pregnancy was associated with increased odds of combined CHD, and the magnitude of the association was comparable with those of $PM_{2.5}$. Smaller particles have higher surface area to mass ratio, carry more toxic constituents, and can more easily penetrate the lung alveoli (Brown et al., 2001; Valavanidis et al., 2008), and thus may exert more deleterious health effects than larger particulates. However, our findings did not support this hypothesis. A possible explanation for the similar effects of PM_1 with $PM_{2.5}$ might be the high $PM_1/PM_{2.5}$ ratio (about 82%; data not shown). It is difficult to directly compare our results with other studies as PM_1 is atypical to consider.

With regard to CHD subtypes, we observed that air pollutants were not associated with VSD, which is one of the most common CHD subtypes. There are already 19 studies evaluating VSD with maternal exposure to PM_{10}, $PM_{2.5}$, and/or NO_2 (Table S1 in the supplement), and most of them found no association with $PM_{2.5}$, which are consistent with our findings. We also detected a positive association between air pollutants and TGA. Ten prior studies have investigated TGA with maternal exposure to PM_{10}, $PM_{2.5}$, and/or NO_2 (Table S1 in the supplement). However, most of the studies found no association, and only one study (Padula et al., 2013), consistent with our findings, reported a positive association with maternal exposure to $PM_{2.5}$ during first months of pregnancy. To our knowledge, we are the first to report a significant association between maternal air pollution exposure and DORV. Two prior studies investigated DORV but both failed to find an association (Huang et al., 2019; Padula et al., 2013). Unexpectedly, we found an inverse association between air pollutants and ASD. There have been 14 published studies concerning ASD with different air pollutants (Table S1 in the supplement). Most of these studies reported either positive or null associations, and only two studies (Padula et al., 2013; Stingone et al., 2014) confirmed our findings showing reduced odds of ASD with increasing $PM_{2.5}$ exposure during pregnancy. The inverse associations might be attributable to methodological limitations and confounding factors, but they could also be due to the "air pollution paradox" that air pollutants exposure may increase the proportion of early spontaneous abortion and selective survival of more viable fetuses, which in turn could cause an inverse association in epidemiological studies (Ritz, 2010).

Several mechanisms have been proposed to explain the relationship between air pollutants and CHD. Migration of crest cells, septation of the ventricles and outflow tracts, and the formation of the endocardial tube are critical stages of cardiac development in the first trimester (Gittenberger-de et al., 2005). Pregnant women exposed to PM showed increased markers of oxidative stress, which have been documented to alter neural cell migration and result in outflow tract defects (Ornoy, 2007; Qi et al., 2014). Also, evidence has indicated that maternal exposure to particles can increase blood viscosity (Qi et al., 2014), induce impairment of vascular endothelial function (Valkonen et al., 2001), and result in an inflammatory condition in the placenta, which affect placenta function, and thus contribute to cardiac malformation

(Balansky et al., 2013). In addition, growing evidence proves that exposure to air pollutants could cause epigenetic alternations and gene expression (Teng et al., 2016), which are closely related to CHD (Avissar-Whiting et al., 2010; Bollati et al., 2010). A very recent study even reported that mothers' residential ambient particulates exposures could be transported towards the fetus (Bove et al., 2019), which provided the direct evidence on detrimental effects of maternal air pollution exposure from early life onwards. Other proposed mechanisms included tissue hypoxia and modified functions of trophoblast cells (Inoue et al., 2004).

Our study has several strengths. First, we included a large and population-based representative sample with high response rate. Second, we employed uniform criteria to clinically confirm a cardiac defect, and an expert panel of clinicians to rigorously review medical chart data and to maximize the validity of case classification. Third, we used an advanced model to estimate individual-level air pollutants. Compared to most prior studies using air pollution data from fixed monitoring stations, our exposure assessment reduced exposure misclassification bias. In addition, we estimated PM_1 exposure and assessed its effects on CHD, which was scarcely monitored by fixed monitoring stations. Finally, we incorporated a rich set of confounders to obtain more precise estimates, and a series of sensitivity analyses indicated that our results were robust.

Our study also has several limitations. First, the case-control design is limited in identifying a temporal sequence between exposure and outcome, which thus reduced its ability of inferring causal relationship. However, maternal air pollution exposure during pregnancy is prior to CHD cases in newborns, thus the possibility of reverse causality is very low. Second, recall bias is always possible in case-control study. However, we used several strategies to reduce the likelihood of misclassification. For instance, we conducted the interviews with mothers when the babies were younger than one year, and used a pregnancy calendar in conjunction with the questionnaire to help the mothers in remembering major milestones of pregnancy. We designed multilevel structured questionnaire with repeated questions to improve recall and classification and assess reliability. Third, while we used an advanced model to evaluate individual-level air pollution concentrations, these exposures can be affected by measurement error issues mainly from the following four sources. The first source is that we used address at the time of delivery to estimate maternal exposures to air pollutants that occurred during pregnancy. Misclassification is possible if mothers changed their residences during pregnancy. However, a prior cohort study in China reported that only 2.6% of the mothers moved during pregnancy (Zhang et al., 2016). The second source is that the assignment of air pollution concentrations is based on residential address, which does not capture exposure during times away from the home. The third source is that we did not have data on time spent outdoors and did not take into account indoor air pollution. The fourth source is that the adjusted R^2 of some pollutants, especially PM_1, was low. Finally, we only included infants aged less than one year old, which is helpful for minimizing the recall bias of pregnancy life styles. However, this could also cause selection bias.

In summary, our study indicates that exposure to PM and NO_2 during the pregnancy, especially the first trimester, was consistently associated with increased odds of CHD combined. Well-designed longitudinal studies with more detailed exposure assessment are warranted to validate our findings.

CRediT authorship contribution statement

Bo-Yi Yang: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition. **Yanji Qu:** Conceptualization, Methodology, Formal analysis, Visualization, Software, Writing - review & editing. **Yuming Guo:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Iana Markevych:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Joachim Heinrich:** Methodology, Validation, Writing - review & editing. **Michael S. Bloom:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Zhipeng Bai:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Luke C. Knibbs:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Shanshan Li:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Gongbo Chen:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Bin Jalaludin:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Lidia Morawska:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Meng Gao:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Bin Han:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Yunjiang Yu:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Xiao-Xuan Liu:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Yanqiu Ou:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Jinzhuang Mai:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Xiangmin Gao:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Yong Wu:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Zhiqiang Nie:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Xiao-Wen Zeng:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Li-Wen Hu:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Xubo Shen:** Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Yuanzhong Zhou:** Validation, Investigation, Data curation, Writing - review & editing. **Shao Lin:** Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Xiaoqing Liu:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing, Funding acquisition, Resources, Supervision, Project administration. **Guang-Hui Dong:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition, Resources, Supervision, Project administration.

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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106548.

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