Ambient air pollution and congenital heart defects in Lanzhou, China

2015 Environ. Res. Lett. 10 074005

(http://iopscience.iop.org/1748-9326/10/7/074005)

Environmental Research Letters

CrossMark

OPEN ACCESS

RECEIVED
6 January 2015

REVISED
28 May 2015

ACCEPTED FOR PUBLICATION
29 May 2015

PUBLISHED
8 July 2015

LETTER

Ambient air pollution and congenital heart defects in Lanzhou, China

Lan Jin[1,6], Jie Qiu[2], Yaqun Zhang[3], Weitao Qiu[2], Xiaochun He[2], Yixuan Wang[2], Qingmei Sun[2], Min Li[4], Nan Zhao[5], Hongmei Cui[2], Sufen Liu[2], Zhongfeng Tang[2], Ya Chen[2], Li Yue[2], Zhenqiang Da[2], Xiaoying Xu[2], Huang Huang[5], Qing Liu[2,7], Michelle L Bell[1] and Yawei Zhang[5]

[1] Yale University, School of Forestry and Environmental Studies, New Haven, CT, US
[2] Gansu Provincial Maternity and Child Care Hospital, Lanzhou, Gansu, People's Republic of China
[3] Gansu Academy of Environmental Sciences, Lanzhou, Gansu, People's Republic of China
[4] Gansu Provincial Environmental Monitoring Central Station, Lanzhou, Gansu, People's Republic of China
[5] Yale University, School of Public Health, New Haven, CT, US
[6] Lan Jin, 195 Prospect Street, New Haven, CT 06511.
[7] Dr Qing Liu, 143 North Road Qilihe District, Lanzhou, Gansu Province 730050, China.

E-mail: lan.jin@yale.edu **and** 2305470816@qq.com

Keywords: air pollution, birth defect, China, congenital heart defect, NO_2, PM_{10}, SO_2

Supplementary material for this article is available online

Abstract

Congenital heart defects are the most prevalent type of birth defects. The association of air pollution with congenital heart defects is not well understood. We investigated a cohort of 8969 singleton live births in Lanzhou, China during 2010–2012. Using inverse distance weighting, maternal exposures to particulate matter with diameters $\leqslant 10\ \mu m$ (PM_{10}), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) were estimated as a combination of monitoring station levels for time spent at home and in a work location. We used logistic regression to estimate the associations, adjusting for maternal age, education, income, BMI, disease, folic acid intake and therapeutic drug use, and smoking; season of conception, fuel used for cooking and temperature. We found significant positive associations of Patent Ductus Arteriosus (PDA) with PM_{10} during the 1st trimester, 2nd trimester and the entire pregnancy (OR $_{1st\ trimester} = 3.96$, 95% confidence interval (CI): 1.36, 11.53; OR $_{2nd\ trimester} = 3.59$, 95% CI: 1.57, 8.22; OR $_{entire\ pregnancy} = 2.09$, 95% CI: 1.21, 3.62, per interquartile range (IQR) increment for PM_{10} (IQR = 71.2, 61.6, and 27.4 $\mu g\ m^{-3}$, respectively)), and associations with NO_2 during 2nd trimester and the entire pregnancy (OR $_{2nd\ trimester} = 1.92$, 95% CI: 1.11, 3.34; OR $_{entire\ pregnancy} = 2.32$, 95% Cl: 1.14, 4.71, per IQR increment for NO_2 (IQR = 13.4 and 10.9 $\mu g\ m^{-3}$, respectively)). The associations for congenital malformations of the great arteries and pooled cases showed consistent patterns. We also found positive associations for congenital malformations of cardiac septa with PM_{10} exposures in the 2nd trimester and the entire pregnancy, and SO_2 exposures in the entire pregnancy. Results indicate a health burden from maternal exposures to air pollution, with increased risk of congenital heart defects.

1. Introduction

A growing body of literature links maternal exposure to air pollution to adverse birth outcomes, including low birth weight, preterm births, intrauterine growth retardation and birth defects [1–5]. Birth defects are a leading cause of infant death and disability later in life [6]. The most prevalent group of birth defects, congenital heart defects, has the highest prevalence in Asia (i.e., 9.3 per 1000 live births) [7]. However, no previous study has been conducted in Asia to investigate the relationship between congenital heart defects and air pollution, despite high pollution levels in this region. Studies on this issue were mainly conducted in western countries and provided inconsistent results [8–20], which might be due to differences in the classification of subgroups of congenital heart defects, the exposure window selection, exposure assessment and adjustments for confounding factors. In light of the inconclusive association between ambient air

pollution and congenital heart defects as well as the lack of studies in areas with both high prevalence of congenital heart defects and high air pollution levels, we conducted a study in Lanzhou, China to fill this gap. To address the challenges of a lack of standardized methodology in previous literature, we included multiple pollutants and exposure windows, and conducted extensive sensitivity analyses to test the validity of our results. In addition, detailed information on residential mobility and other risk factors of congenital heart defects was available in our cohort to improve exposure and risk assessment.

Lanzhou, located in Northwest China, is the capital and largest city of Gansu Province, with area of 5058 mile^2 and 3.6 million residences. It is also a transportation hub linking the East and the West of China. According to a 2011 World Health Organization report, Lanzhou was the most polluted city in China [21]. Sand storms, emissions from factories and traffic result in high levels of air pollution. Moreover, the city center is surrounded by mountains and hills that rise to 500–600 m. This trough-shaped topography traps air pollutants at the ground level, resulting in well-documented poor air quality [22]. Previous analysis of the characteristics of ambient air pollution in Lanzhou during the study period identified that PM_{10} concentrations exceeded health-based regulations and guidelines [23–25] and high levels of air pollution in Lanzhou were associated with increased risk of health outcomes such as hospital admissions for respiratory disease [26].

The objective of this study is to investigate whether maternal exposures to PM_{10}, NO_2 and SO_2 are associated with elevated risks of congenital heart defects in Lanzhou, China. This study is the first to investigate the relationship between birth defects and ambient air pollution in China. We provide analysis of birth defects in relation to levels of ambient air pollution that are higher than many other locations, but relevant globally, especially in areas with rapid urbanization and expanding industry and transportation.

2. Materials and methods

2.1. Study population

We recruited 10 542 women who gave birth at Gansu Provincial Maternity and Child Care Hospital in Lanzhou, China in 2010–2012. The process of enrollment was described elsewhere [27]. Written consent was obtained and then in-person interviews were conducted by trained study interviewers at the hospital. By means of a standardized and structured questionnaire, women provided detailed information on demographics (i.e., residential history, education, family income, and access to prenatal health education), medical and reproductive history (e.g., any conditions of hypertension, coronary heart disease, diabetes, HBV infection; any previous pregnancy history) and lifestyle choices (e.g., active or passive smoking, alcohol drinking, tea consumption, diet, physical exercises and fuel used for cooking). Birth outcomes and information on maternal complications (e.g., gestational age, birth weight, and defects; any gestational hypertension and preeclampsia) were abstracted from the medical records. Congenital heart defects (N = 73) were ascertained if any of the following subtypes were confirmed: Q20–Q28 (International Classification of Diseases (ICD)-10 code). The cases were diagnosed shortly after birth.

Among the 10 542 women who completed the questionnaires, we excluded women who lived outside Lanzhou ($n = 1344$), had multiple births ($n = 323$), had infants with other birth defects ($n = 174$) or had stillbirths ($n = 53$). Then we excluded women living further than 50 km to the closest air pollution monitor ($n = 127$) [14]. Finally, 8729 singleton live births were included in the analysis. Congenital heart defects were the most common type of birth defect in this cohort (prevalence: 8.4 per 1000 singleton live births). Infants included in the analyses ($n = 8729$) include 73 pooled cases (any type or multiple congenital heart defects), 54 congenital malformations of the great arteries, 19 congenital malformations of cardiac septa, 1 congenital malformations of cardiac chambers and connections, and 7 other congenital malformations of heart (supplementary table S5).

2.2. Exposure assessment

Daily average concentrations of ambient PM_{10}, SO_2, and NO_2 were obtained from 4 air monitoring stations in Lanzhou, operated by the Lanzhou Environmental Monitoring Bureau (figure 1). These three pollutants were the only ambient air pollutants routinely measured in Lanzhou before 2013. Two monitoring stations, Xigu and Huanghebei, had 48 months of daily observations (April 2009–March 2013) in the study period. The other two stations, Xizhan and Tieluju, provided observations for 27 months (January 2011–March 2013). The monitoring data from the 2 monitors covering the full study period were used in the main analysis.

The full residential history including the start and stop dates for each residence was obtained, so residential mobility was taken into account. If a woman had more than one address during an exposure window, the exposure estimates were weighted based on the number of days at each residence. Further we considered exposures at work place locations.

First, the date of conception was calculated based on the date of birth and gestational age. Daily average concentrations of air pollutants were spatially interpolated using inverse distance weighting (IDW) to assign daily exposures at each residence and work location. IDW is an interpolation method to assign pollution levels to unknown points based on known monitoring data. The following is the IDW formula

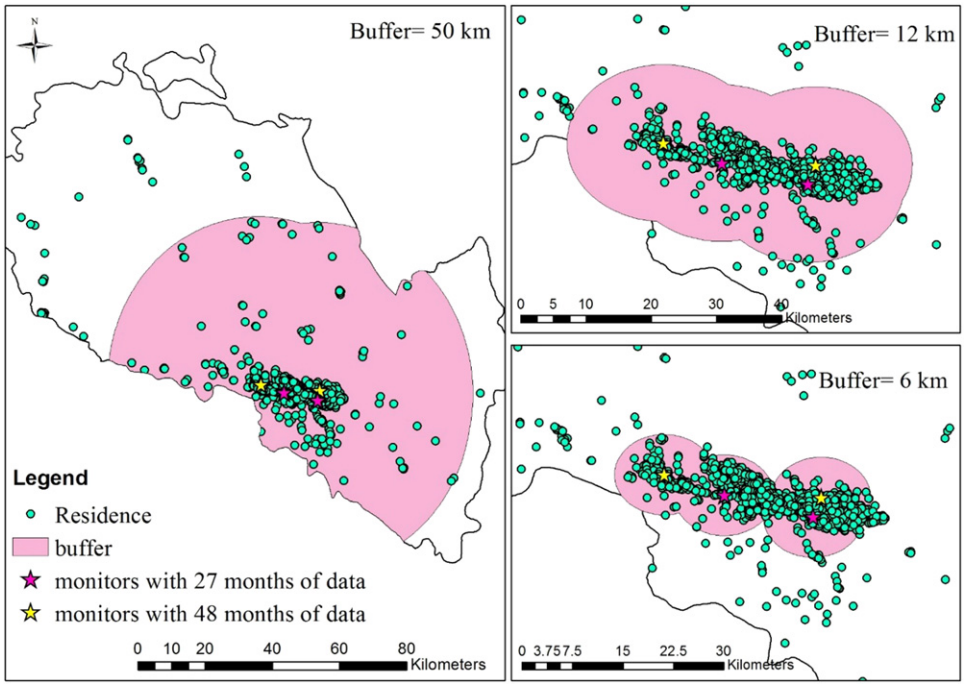

Figure 1. Locations of monitors, distribution of residences of births and buffers of 6, 12 and 50 km from monitors ($n = 8969$).

for pollution levels at point (x, y): $\hat{z}(x, y) = \frac{\sum_i zidi^{-1}}{\sum_i di^{-1}}$, where z_i is the pollution levels at the ith monitor and d_i is the distance from the ith monitor to the point of interest (x, y). Then, exposures were time-weighted averaged as 2/3 of time at home and 1/3 of time at work. Daily exposures were averaged over four exposure windows: week 3–8, 1st, 2nd trimester and entire pregnancy. Week 3–8 of pregnancy is often considered a critical window during which the fetus is susceptible to the development of congenital heart defects [28]. The 1st and 2nd trimesters have been analyzed separately in previous studies investigating congenital anomalies and air pollution [15, 16, 29]. In summary, for each pregnancy, 12 variables were estimated for combinations of 3 pollutants (PM_{10}, SO_2, and NO_2) and 4 exposure windows during pregnancy (week 3–8 of pregnancy, the 1st, 2nd trimester and entire pregnancy).

2.3. Statistical analysis

The associations between maternal exposures to air pollution and risk of congenital heart defects were estimated by logistic regression models. The outcome groups included in the models were pooled cases (ICD 10: Q20–28), congenital malformations of great arteries (ICD 10: Q25), congenital malformations of cardiac septa (ICD 10: Q21), and isolated cases of Patent Ductus Arteriosus (PDA) (ICD 10: Q250). PDA is the most prevalent subtype of congenital malformations of the great arteries in our cohort. Exposure variables were included in the models as continuous variables, with separate models for each pollutant. We included the following covariates in the fully adjusted models: maternal age (<25, 25–30, 30–35, ⩾35 years), maternal education (less than high school, finished high school, more than high school), monthly family income (<2000, 2000–4000, ⩾4000 RMB), mother's body mass index (BMI) (<24, ⩾24 kg m^{-3}) [30], folic acid intake during the 1st trimester (yes/no), therapeutic drug intake (yes/no), maternal illness (yes/no), smoking status including passive and active smoking (yes/no), fuel used for cooking (gas and electricity or no cooking/other), temperature and season of conception [spring (March–May), summer (June–August), fall (September–November), or winter (December–February)].

Periconceptional intake of folic acid containing multiple vitamins has been associated with a reduced risk of congenital heart defects [31]. On the other hand, some therapeutic drugs might increase risk of birth defects if ingested during pregnancy [31]. A woman was considered to ingest therapeutic drugs if she took at least one category of the following drugs: thalidomide, antibiotics, antiviral agents, antifungal therapies, anticonvulsants, lithium, benzodiazepines, sympathomimetics, corticosteroids, nonsteroidal anti-inflammatory drugs, female hormones, or angiotension-converting enzyme inhibitors. Maternal illness was used as a binary variable to adjust for the overall health status of the mothers. The following diseases assessed by the survey were considered: cardiovascular disease, respiratory diseases, renal diseases, thyroid diseases, anemia, HBV infection and cirrhosis.

Extensive sensitivity analyses have been conducted to test the validity of our results. 1) To assess the influence of exposure at work, maternal exposures

Table 1. Summary statistics of daily maternal exposures[a] in Lanzhou, 2009–2012 ($\mu g\ m^{-3}$).

Exposure windows	PM_{10} Mean (IQR)	NO_2 Mean (IQR)	SO_2 Mean (IQR)
Weeks 3–8	137.5 (79.8)	44.2 (14.4)	57.0 (57.6)
First trimester	137.9 (71.2)	44.1 (13.0)	57.1 (56.1)
Second trimester	142.3 (61.6)	43.3 (13.4)	59.0 (62.3)
Entire pregnancy	140.0 (27.4)	42.5 (10.9)	56.4 (19.2)

Abbreviations: IQR, interquartile range.

[a] The exposures were estimated using the primary approach (i.e., 2 monitors covering the entire period of study). The exposures were estimated for women living within 50 km of a monitor ($n = 8729$).

calculated only at home were included in the logistic regression models. 2) Children with other defects were included in the analyses. 3) We explored risks associated with exposure levels higher than Chinese national air quality standard [23]. The fraction of days exceeding the daily Chinese air quality standards were calculated for each woman during each exposure window. 4) We conducted the analyses for women who lived close to the monitors (<6 or 12 km of a monitor) (supplementary figure S1). 5) Maternal exposures were divided into tertiles to explore the hypothesis of a linear exposure-response relationship. 6) We repeated main analyses using data from all 4 monitors, that is, daily exposures were calculated based on 2 monitors before 1 January 2011, and based on all 4 monitors for later days. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Summary of air pollution exposure and the study subjects

The average concentrations of PM_{10}, NO_2, and SO_2 were 143.8 $\mu g\ m^{-3}$, 41.6 $\mu g\ m^{-3}$, and 54.5 $\mu g\ m^{-3}$, respectively. Average air pollution concentrations from the 4 monitoring stations were similar, indicating low spatial heterogeneity of air pollution at the city level [26]. The correlations between the three pollutants from the 2 monitors covering the full study period were weak (supplementary table S1).

The average and IQR of maternal exposures to PM_{10}, NO_2, and SO_2 during each exposure window are shown in table 1. The IQR corresponds to the increments in the following results when air pollution exposures were included as continuous variables. Exposures during weeks 3–8 of pregnancy were highly correlated with exposures in the 1st trimester (table 2). Exposures were significantly higher among the infants with, than without congenital heart defects (p-value <0.05) (table 3).

The characteristics of the study population are shown in table 3. Distribution of maternal age, folic acid intake, therapeutic drug use, gestational weeks, and maternal illness before pregnancy were significantly different between infants without congenital heart defects and pooled cases (p-value <0.05). Mothers whose infants had any congenital heart defects were more likely to be older than 35 (15.1% versus 6.6%), or have an illness (6.9% versus 2.7%) than mothers whose infants did not have congenital heart defects. Folic acid intake during the 1st trimester was more common among mothers with healthy infants (67.5% versus 56.4%). Therapeutic drug use during pregnancy was more common in women whose infants had any congenital heart defects (9.6% versus 5.2%). Congenital malformations of the great arteries and cardiac septa showed similar patterns in the pooled cases.

3.2. Associations between air pollution and congenital heart defects

The adjusted ORs (95% CI) for congenital heart defects associated with maternal exposure to air pollution are shown in table 4. In the fully adjusted model, positive associations were observed between isolated PDA and an IQR increase in PM_{10} exposures during the 1st, 2nd trimester and the entire pregnancy ($OR_{\text{1st trimester}} = 3.96$, 95% CI: 1.36, 11.53; $OR_{\text{2nd trimester}} = 3.59$, 95% CI: 1.57, 8.22; $OR_{\text{entire pregnancy}} = 2.09$, 95% CI: 1.21, 3.62); and an IQR increase in NO_2 exposure during the 2nd trimester and entire pregnancy ($OR_{\text{2nd trimester}} = 1.92$, 95% CI: 1.11, 3.34; $OR_{\text{entire pregnancy}} = 2.32$, 95% Cl: 1.14, 4.71). No associations were found during weeks 3–8 of pregnancy. The results for congenital malformations of the great arteries and pooled cases showed similar patterns. Congenital malformations of cardiac septa were positively associated with PM_{10} exposures during the 2nd trimester and the entire pregnancy ($OR_{\text{2nd trimester}} = 5.51$, 95% CI: 1.36, 22.35; $OR_{\text{entire pregnancy}} = 2.70$, 95% CI: 1.11, 6.57, for IQR increment), and with SO_2 exposures during the entire pregnancy ($OR_{\text{entire pregnancy}} = 5.16$, 95% CI: 1.01, 26.26, for IQR increment).

The analyses using exposures calculated only at home, rather than at work and home, showed similar results (table 5). The analyses including children with other defects also showed similar results (table 6). On average, during the entire pregnancy Chinese daily air quality standards were exceeded for 32.3, 6.2 and 5.3% of days for PM_{10}, NO_2 and SO_2, respectively. For isolated PDA, positive associations were found for the fraction of days with PM_{10} levels exceeding daily national standards during the 2nd trimester and the entire pregnancy (table 7). During the entire pregnancy, for every 40.5% (IQR) increase in the fraction of days with PM_{10} levels exceeding 150 $\mu g\ m^{-3}$, the odds of having an infant with PDA would be doubled (OR = 2.00; 95% CI: 1.16, 3.45). For pooled cases and congenital malformations of the great arteries, positive

Table 2. Correlation coefficients between maternal exposures during different exposure windows[a].

		1st trimester	2nd trimester	Entire pregnancy
	Weeks 3–8	0.94	0.06	0.22
PM_{10}	1st trimester		0.15	0.30
	2nd trimester			0.79
	Weeks 3–8	0.93	−0.05	0.44
NO_2	1st trimester		0.07	0.53
	2nd trimester			0.67
	Weeks 3–8	0.97	−0.11	−0.05
SO_2	1st trimester		0.02	0.05
	2nd trimester			0.79

[a] The exposures were estimated for women living within 50 km of a monitor ($n = 8729$) using 2 monitors covering the entire period of study.

associations were found for the fraction of days with PM_{10} levels exceeding 150 $\mu g\ m^{-3}$during the 1st, 2nd and entire pregnancy (table 7).

Most of the women lived within 12 km of a monitor. The number of cases and total births living within 6, 12 and 50 km of a monitor, and the distribution of distance between residence and the closest monitor are shown in supplementary table S3. The sensitivity analyses for women living within 6 or 12 km of a monitor showed consistent results (results for isolated PDA shown in figure 2). Linear exposure–response patterns were confirmed between isolated PDA and PM_{10} and NO_2 exposures during the 2nd trimester (p for trend <0.05) (figure 3). The sensitivity analyses using monitoring data from all 4 monitors showed consistent results (supplementary table S2).

4. Discussion

In this birth cohort study, we found positive associations of PM_{10} and NO_2 exposures during the 2nd trimester and entire pregnancy with isolated PDA, congenital malformations of the great arteries, and pooled cases in Lanzhou, China in 2009–2012. The association for PM_{10} exposures in the 1st trimester was also significant. We did not find significant associations for exposures during weeks 3–8 of pregnancy. Results from sensitivity analyses were consistent.

Mechanisms of the teratogenicity of air pollutants remains unclear, but several hypotheses have been proposed for the effects of air pollutants on fetal development, including oxidative stress, pulmonary and placental inflammations, increased blood coagulation and viscosity, and oxidation of lipids and proteins by NO_2, as reviewed by Polichetti *et al* [2]. Congenital anomalies may share the similar etiological pathway with early fetal growth [1].

Our results were consistent with a meta-analysis on air pollution and congenital anomalies, which found positive PM_{10} associations with coarctation of the aorta (CoA) (a type of congenital malformations of the great arteries), Ventricular Septal Defects (VSD) and Atrial Septal Defects (ASD) (types of congenital malformations of cardiac septa); and associations of NO_2 with CoA [1]. We also compared our results with 13 previous original epidemiologic studies investigating the relationship between air pollution exposures and congenital heart defects (table 8). These studies were identified by searching three scientific literature databases: Web of Science, Scopus, and PubMed [32–34]. The final search was conducted on 27 March 2015. Searches were performed for the following terms: 1) at least one of the following: 'air pollution', 'air pollutant', 'air pollutants', 'particulate matter', PM_{10}, SO_2, or NO_2; and 2) 'heart defect*' or 'cardiac defect*', where * represents any combination of characters. Studies only investigating combined congenital anomalies as a composite outcome variable were not included in this table.

The ORs for isolated PDA (the most prevalent subtype of arteries malformations in our cohort) were reported in three studies [8, 15, 19]. One study found a positive association for PM_{10}, consistent with our results [19]. Coarctation of the aorta, another subtype of artery malformation, was found to be positively associated with NO_2 and SO_2 [13, 17, 18]; this subtype was not found in our cohort. Pooled artery defects were investigated in five studies, with none finding significant associations, which is not consistent with our result [9–13]. Pooled septal defects were investigated in ten previous studies [8–14, 16, 18, 19], which found positive associations for PM_{10} with ASD, and perimembranous VSD [12, 14, 18]. This is consistent with our result during the entire pregnancy. However, septal defects had a small sample size (14 with complete covariate information). The ORs for pooled cases were reported in six studies [8, 9, 11, 15–17]. Our results are consistent with a study in Israel [8], which also found positive associations for PM_{10}; however, no studies showed positive associations for NO_2 or SO_2. In fact, SO_2 was found to have protective effects in two studies [9, 15].

Air pollution levels in Lanzhou were substantially higher than levels in Atlanta (US), Brisbane (Australia), Barcelona (Spain), four regions in England,

Table 3. Characteristics of Infants with and without congenital heart defects, Lanzhou, 2010–2012[a].

Characteristic	Infants without congenial heart defects ($n = 8656$)[b]	Pooled congenital heart defects ($n = 73$)[b]	Congenital malformations of great arteries ($n = 54$)[c]	Congenital malformations of cardiac septa ($n = 19$)[d]
Infant's gender				
Male	4528 (52.3)	40 (54.8)	29 (53.7)	13 (68.4)
Female	4099 (47.4)	32 (43.8)	25 (46.3)	6 (31.6)
Missing	29 (0.3)	1 (1.4)	0	0
Maternal age (years)				
⩽25	1788 (20.7)	17 (23.3)	16 (29.6)	1 (5.3)
25–30	4447 (51.4)	37 (48.0)	23 (42.6)	14 (76.7)
30–35	1853 (21.4)	10 (13.7)	7 (13)	3 (15.8)
>35	568 (6.6)	11 (15.1)	8 (14.8)	1 (5.3)
Maternal education				
Less than high school	1502 (17.4)	21 (28.8)	15 (27.8)	5 (26.3)
Finished high school	1515 (17.5)	13 (17.8)	11 (20.4)	3 (15.8)
More than high school	5486 (63.4)	38 (52.1)	27 (50.0)	10 (52.6)
Missing	153 (1.8)	1 (1.4)	1 (1.9)	1 (5.3)
Monthly family income (RMB)				
<2000[e]	1769 (20.4)	20 (27.4)	16 (19.6)	6 (31.6)
2000–4000	4166 (48.1)	28 (38.4)	18 (33.3)	9 (47.4)
⩾4000	1893 (21.9)	15 (20.6)	12 (22.2)	0
Missing	835 (9.6)	10 (13.7)	8 (14.8)	4 (21.1)
Mother's BMI (kg m^{-3})				
<24[f]	7522 (86.9)	59 (80.8)	43 (79.6)	16 (84.2)
⩾24	897 (10.4)	10 (13.7)	8 (14.8)	2 (10.5)
Missing	237 (2.7)	4 (5.5)	3 (5.6)	0
Maternal folic acid intake in the first trimester				
Yes	5840 (67.5)	41 (56.2)	25 (46.3)	10 (52.6)
No	2816 (32.5)	32 (43.8)	29 (53.7)	9 (47.4)
Maternal therapeutic drug intake during pregnancy				
Yes	447 (5.2)	7 (9.6)	5 (9.3)	3 (15.8)
No	8206 (94.8)	65 (89.0)	49 (90.7)	16 (84.2)
Missing	3 (0.1)	1 (1.4)	0	0
Maternal illness				
Yes	230 (2.7)	5 (6.9)	4 (7.4)	2 (10.5)
No	8426 (97.3)	68 (93.2)	50 (92.6)	17 (89.5)

Table 3. (Continued.)

Characteristic	Infants without congenial heart defects ($n = 8656$)[b]	Pooled congenital heart defects ($n = 73$)[b]	Congenital malformations of great arteries ($n = 54$)[c]	Congenital malformations of cardiac septa ($n = 19$)[d]
Maternal smoking				
Yes	13 (17.8)	1630 (18.8)	11 (20.4)	0
No	60 (82.2)	7026 (81.2)	43 (79.6)	19 (100)
Cooking fuel				
Gas and electricity or not cooking	58 (79.5)	7663 (88.5)	43 (79.6)	15 (79.0)
Other	5 (6.9)	347 (4.0)	2 (3.7)	1 (5.3)
Missing	10 (13.7)	646 (7.5)	9 (16.7)	3 (15.8)
Season of conception				
Spring	13 (17.8)	1814 (21.0)	6 (11.1)	4 (21.1)
Summer	28 (38.4)	2497 (28.9)	22 (40.7)	8 (42.1)
Fall	22 (30.1)	2367 (27.4)	17 (31.5)	5 (26.3)
Winter	10 (13.7)	1978 (22.9)	9 (16.7)	2 (10.5)
Pregnancy mobility				
Move at least once	266 (3.1)	2 (2.7)	1 (1.8)	1 (5.3)
Did not move	8390 (96.9)	71 (97.3)	53 (98.2)	18 (94.7)
Working during pregnancy				
Work	3815 (44.1)	31 (42.5)	21 (38.9)	9 (47.4)
Not work	4841 (55.9)	42 (57.5)	33 (61.1)	10 (52.6)
Gestational exposure				
PM_{10}	139.9 (19.2)	151.3 (23.8)	152.6 (24.3)	155.0 (24.2)
NO_2	42.4 (6.9)	44.9 (5.9)	44.9 (5.6)	45.5 (4.9)
SO_2	56.4 (12.9)	60.7 (12.9)	61.2 (11.5)	62.6 (11.1)

[a] Table values are *n* (column %) for categorical variables and mean (SD) for continuous variables. Percentages may not sum to 100% due to rounding. The primary analysis included women living within 50 km of a monitor ($n = 8729$).

[b] Congenital malformations of the great arteries is a subgroup of congenital heart defects. They include 52 cases with Patent ductus arteriosus, and 2 cases with both Patent ductus arteriosus and Stenosis of pulmonary artery.

[c] Patent Ductus Arteriosus (PDA) is the most prevalent subtype of malformations of the great arteries in this cohort. Isolated cases of PDA are the cases with PDA only.

[d] 1RMB ~ = 0.16USD.

[e] BMI cut-off point of overweight is for people living in mainland China.

and the Tel-Aviv region in Israel, except for NO_2 in Barcelona [8, 11, 13, 17, 19]. PDA is the most prevalent subtype in our cohort (52.7 per 10 000), which was higher than that reported in previous studies (Texas, US: 2.5 per 10 000; four regions, UK, 4.6 per 10 000; the Tel-Aviv region, Israel: 12.6 per 10 000; Guangdong Province, China: 20.1 per 10 000) [8, 15, 19, 35]. These differences might contribute to the variation in results.

We found positive associations for PM_{10} with isolated PDA, pooled artery defects, and pooled cases during the 1st and 2nd trimester, supported by extensive sensitivity analyses. This is consistent with a Korean study finding the same pattern for pooled

Table 4. Adjusted ORs[a] (95% CI) for congenital heart defects associated with IQR[b] increases in air pollution exposures during weeks 3–8, the 1st, 2nd, 3rd trimesters and entire pregnancy[c] in Lanzhou, 2010–2012.

		PM_{10}	NO_2	SO_2
Outcome groups	Exposure windows	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pooled congenital heart defects ($N = 73$)	Weeks 3–8	1.42 (0.70, 2.87)	1.21 (0.78, 1.89)	0.78 (0.28, 2.17)
	1st trimester	3.10 (1.28, 7.51)	1.49 (0.91, 2.44)	0.54 (0.15, 2.02)
	2nd trimester	4.23 (2.11, 8.50)	1.86 (1.18, 2.93)	0.87 (0.16, 4.62)
	Entire pregnancy	2.28 (1.45, 3.60)	2.26 (1.26, 4.08)	1.21 (0.51, 2.86)
Congenital malformation of great arteries ($N = 54$)	Weeks 3–8	1.83 (0.83, 4.03)	1.18 (0.72, 1.94)	0.89 (0.28, 2.84)
	1st trimester	4.23 (1.53, 11.65)	1.45 (0.83, 2.54)	0.69 (0.26, 1.81)
	2nd trimester	4.00 (1.80, 8.87)	1.99 (1.18, 3.36)	0.87 (0.12, 6.22)
	Entire pregnancy	2.33 (1.37, 3.97)	2.16 (1.12, 4.18)	1.27 (0.47, 3.48)
Congenital malformation of cardiac septa ($N = 19$)	Weeks 3–8	1.39 (0.35, 5.50)	0.94 (0.36, 2.42)	1.46 (0.22, 9.94)
	1st trimester	2.43 (0.43, 13.90)	0.95 (0.34, 2.63)	0.84 (0.14, 4.91)
	2nd trimester	5.51 (1.36, 22.35)	1.58 (0.65, 3.80)	2.57 (0.10, 63.78)
	Entire pregnancy	2.70 (1.11, 6.57)	1.53 (0.52, 4.50)	5.16 (1.01, 26.26)
Isolated cases of patent ductus arteriosus[d] ($N = 46$)	Weeks 3–8	1.72 (0.74, 4.00)	1.27 (0.76, 2.13)	0.68 (0.20, 2.39)
	1st trimester	3.96 (1.36, 11.53)	1.69 (0.94, 3.04)	0.49 (0.10, 2.38)
	2nd trimester	3.59 (1.57, 8.22)	1.92 (1.11, 3.34)	0.60 (0.08, 4.71)
	Entire pregnancy	2.09 (1.21, 3.62)	2.32 (1.14, 4.71)	0.86 (0.29, 2.53)

[a] Adjusted for: maternal age, maternal education, monthly family income, mother's body mass index, folic acid intake during the 1st trimester, therapeutic drug intake, any maternal diseases, smoking status including passive and active smoking, fuel for cooking, season of conception and temperature. For congenital malformations of cardiac septa, covariates of maternal age, income, smoking, and fuels for cooking have categories where the number of cases were ⩽1. Therefore, the following changes were made for these covariates in the models: 1) smoking and fuels for cooking were excluded; 2) maternal age was categorized into two groups (⩽30 and >30); 3) income was categorized into two groups (<2000 and ⩾2000).

[b] IQR: interquartile range of PM_{10}, NO_2, and SO_2 are specific to each exposure window (table 1).

[c] The exposures were estimated for women living within 50km of a monitor ($n = 8729$) using 2 monitors covering the entire period of study.

[d] Patent Ductus Arteriosus (PDA) is the most prevalent subtype of malformations of the great arteries in this cohort. Isolated cases of PDA are the cases with PDA only.

Table 5. Adjusted ORs[a] (95% CI) for congenital heart defects associated with IQR increases in air pollution exposures at home[b] in Lanzhou, 2010–2012.

		PM_{10}	NO_2	SO_2
Outcome groups	Exposure windows	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pooled congenital heart defects ($N = 73$)	Weeks 3–8	1.43 (0.71, 2.88)	1. 19 (0.80, 1.78)	0.80 (0.29, 2.23)
	1st trimester	3.02 (1.26, 7.25)	1.47 (0.90, 2.40)	0.77 (0.15, 4.02)
	2nd trimester	4.01 (2.00, 8.01)	1.81 (1.16, 2.85)	0.78 (0.15, 4.01)
	Entire pregnancy	2.21 (1.40, 3.50)	2.18 (1.22, 3.88)	1.22 (0.53, 2.83)
Congenital malformation of great arteries ($N = 54$)	Weeks 3–8	1.83 (0.84, 4.02)	1.16 (0.71, 1.91)	0.89 (0.28, 2.83)
	1st trimester	4.06 (1.49, 11.06)	1.41 (0.81, 2.47)	0.69 (0.27, 1.79)
	2nd trimester	3.81 (1.73, 8.41)	1.95 (1.16, 3.27)	0.76 (0.11, 5.28)
	Entire pregnancy	2.26 (1.32, 3.87)	2.08 (1.09, 3.98)	1.24 (0.47, 3.31)
Congenital malformation of cardiac septa ($N = 19$)	Weeks 3–8	1.40 (0.36, 5.49)	0.99 (0.39, 2.52)	1.61 (0.24, 10.75)
	1st trimester	2.44 (0.44, 13.62)	0.99 (0.36, 2.71)	0.89 (0.15, 5.11)
	2nd trimester	5.11 (1.28, 20.41)	1.52 (0.64, 3.64)	2.28 (0.10, 52.89)
	Entire pregnancy	2.58 (1.05, 6.31)	1.48 (0.51, 4.3)	5.21 (1.06, 25.47)
Isolated cases of patent ductus arteriosus[d] ($N = 46$)	Weeks 3–8	1.73 (0.75, 4.00)	1.26 (0.75, 2.10)	0.69 (0.20, 2.39)
	1st trimester	3.80 (1.32, 10.97)	1.64 (0.92, 2.94)	0.54 (0.19, 1.52)
	2nd trimester	3.42 (1.50, 7.80)	1.88 (1.09, 3.26)	0.52 (0.07, 4.01)
	Entire pregnancy	2.02 (1.16, 3.53)	2.22 (1.11, 4.44)	0.86 (0.30, 2.45)

[a] Adjusted for: maternal age, maternal education, monthly family income, mother's body mass index, folic acid intake during the 1st trimester, therapeutic drug intake, any maternal diseases, smoking status including passive and active smoking, fuel for cooking, season of conception, and temperature. For congenital malformations of cardiac septa, covariates of maternal age, income, smoking, and fuels for cooking have categories where the number of cases were ⩽1. Therefore, the following changes were made for these covariates in the models: 1) smoking and fuels used for cooking were excluded; 2) maternal age was categorized into two groups (⩽30 and >30); 3) income was categorized into two groups (<2000 and ⩾2000).

[b] IQR: interquartile range of PM_{10}, NO_2, and SO_2 are specific to each exposure window (table 1).

[c] The exposures were estimated for women living within 50km of a monitor ($n = 8729$) using 2 monitors covering the entire period of study.

[d] Patent Ductus Arteriosus (PDA) is the most prevalent subtype of malformations of the great arteries in this cohort. Isolated cases of PDA are the cases with PDA only.

Table 6. Adjusted ORs[a] (95% CI) for congenital heart defects associated with IQR[b] increases in air pollution exposures during week 3–8, the 1st, 2nd, 3rd trimesters and entire pregnancy[c] including children with other defects in Lanzhou, 2010–2012.

		PM_{10}	NO_2	SO_2
Outcome groups	Exposure windows	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pooled congenital heart defects ($N = 73$)	Weeks 3–8	1.42 (0.70, 2.88)	1.19 (0.79, 1.78)	0.77 (0.28, 2.17)
	1st trimester	3.09 (1.27, 7.50)	1.49 (0.91, 2.46)	0.56 (0.23, 1.37)
	2nd trimester	4.21 (2.10, 8.45)	1.86 (1.18, 2.93)	0.87 (0.16, 4.67)
	Entire pregnancy	2.32 (1.46, 3.70)	2.26 (1.26, 4.07)	1.20 (0.50, 2.84)
Congenital malformation of great arteries ($N = 54$)	Weeks 3–8	1.84 (0.83, 4.05)	1.17 (0.71, 1.93)	0.88 (0.27, 2.84)
	1st trimester	4.23 (1.53, 11.68)	1.45 (0.83, 2.53)	0.69 (0.26, 1.81)
	2nd trimester	3.98 (1.80, 8.83)	1.99 (1.18, 3.36)	0.87 (0.12, 6.25)
	Entire pregnancy	2.32 (1.36, 3.95)	2.15 (1.11, 4.16)	1.26 (0.46, 3.43)
Congenital malformation of cardiac septa ($N = 19$)	Weeks 3–8	1.40 (0.35, 5.53)	0.94 (0.36, 2.42)	1.46 (0.21, 9.98)
	1st trimester	2.44 (0.43, 13.92)	0.95 (0.34, 2.64)	0.85 (0.14, 4.93)
	2nd trimester	5.49 (1.36, 22.21)	1.58 (0.65, 3.81)	2.61 (0.10, 64.75)
	Entire pregnancy	2.69 (1.11, 6.56)	1.53 (0.52, 4.50)	5.12 (1.01, 25.99)
Isolated cases of patent ductus arteriosus[d] ($N = 46$)	Weeks 3–8	1.72 (0.74, 4.02)	1.27 (0.76, 2.12)	0.68 (0.19, 2.38)
	1st trimester	3.97 (1.36, 11.59)	1.69 (0.94, 3.03)	0.48 (0.10, 2.36)
	2nd trimester	3.58 (1.56, 8.19)	1.92 (1.11, 3.34)	0.59 (0.07, 4.73)
	Entire pregnancy	2.08 (1.20, 3.60)	2.31 (1.14, 4.68)	0.85 (0.29, 2.49)

[a] Adjusted for: maternal age, maternal education, monthly family income, mother's body mass index, folic acid intake during the 1st trimester, therapeutic drug intake, any maternal diseases, smoking status including passive and active smoking, fuel used for cooking, season of conception and temperature. For congenital malformations of cardiac septa, covariates of maternal age, income, smoking, and fuels for cooking have categories where the number of cases were ⩽1. Therefore, the following changes were made for these covariates in the models: 1) smoking and fuels for cooking were excluded; 2) maternal age was categorized into two groups (⩽30 and >30); 3) income was categorized into two groups (<2000 and ⩾2000).

[b] IQR: interquartile range of PM_{10}, NO_2, and SO_2 are specific to each exposure window (table 1).

[c] The exposures were estimated for women living within 50km of a monitor ($n = 8839$) using 2 monitors covering the entire period of study.

[d] Patent Ductus Arteriosus (PDA) is the most prevalent subtype of malformations of the great arteries in this cohort. Isolated cases of PDA are the cases with PDA only.

Table 7. Adjusted ORs for congenital heart defects associated with IQR[a] increase in fraction of days exceeding daily national standards during each exposure window for PM_{10}, NO_2 and SO_2 (150.0 μg m^{-3} for PM_{10}, 80.0 μg m^{-3} for NO_2, 150.0 μg m^{-3} for SO_2)[b].

		PM_{10}	NO_2	SO_2
Outcome groups	Exposure windows	OR (95% CI)	OR (95% CI)	OR (95% CI)
Pooled congenital heart defects ($N = 73$)	Weeks 3–8	1.10 (0.51, 2.40)	1.12 (0.87, 1.44)	1.34 (0.97, 1.84)
	1st trimester	2.53 (1.07, 5.99)	1.38 (0.99, 1.94)	1.26 (0.63, 2.52)
	2nd trimester	6.16 (2.54, 14.95)	1.25 (0.97, 1.61)	0.85 (0.54, 1.34)
	Entire pregnancy	2.28 (1.44, 3.59)	1.79 (0.99, 3.25)	1.20 (0.67, 2.17)
Congenital malformation of great arteries ($N = 54$)	Weeks 3–8	1.48 (0.60, 3.66)	1.05 (0.80, 1.38)	1.09 (0/.83, 1.43)
	1st trimester	3.39 (1.23, 9.35)	1.25 (0.87, 1.80)	0.89 (0.52, 1.52)
	2nd trimester	5.41 (1.94, 15.07)	1.28 (0.95, 1.73)	0.90 (0.48, 1.70)
	Entire pregnancy	2.88 (1.34, 3.88)	1.47 (0.74, 2.93)	0.95 (0.46, 1.93)
Congenital malformation of cardiac septa ($N = 19$)	Weeks 3–8	1.43 (0.31, 6.49)	1.01 (0.59, 1.73)	1.39 (0.45, 4.28)
	1st trimester	3.13 (0.59, 16.65)	1.04 (0.52, 2.09)	1.59 (0.59, 4.24)
	2nd trimester	5.50 (0.97, 31.07)	1.24 (0.75, 2.05)	0.58 (0.18, 1.86)
	Entire pregnancy	2.95 (1.19, 7.32)	1.39 (0.45, 4.28)	3.31 (1.26, 8.69)
Isolated cases of patent ductus arteriosus[c] ($N = 46$)	Weeks 3–8	1.27 (0.49, 3.30)	1.07 (0.81, 1.42)	1.05 (0.77, 1.42)
	1st trimester	2.53 (0.88, 7.29)	1.34 (0.91, 1.96)	0.79 (0.43, 1.45)
	2nd trimester	4.92 (1.68, 14.44)	1.29 (0.92, 1.80)	0.88 (0.45, 1.69)
	Entire pregnancy	2.00 (1.16, 3.45)	1.58 (0.76, 3.24)	0.81 (0.37, 1.76)

[a] The IQR of fraction of days exceeding daily national standards during week 3–8, 1st, 2nd trimester, and entire pregnancy for PM_{10} are 45.2, 40.5, 34.5, 13.1%. The IQR for NO_2 during the above exposure windows are 9.5, 9.5, 8.3, 9.4%. The IQR for SO_2 during the above exposure windows are 7.1, 9.5, 10.7, 3.4%.

[b] The exposures were estimated for women living within 50 km of a monitor ($n = 8729$) using 2 monitors covering the entire period of study.

[c] Patent Ductus Arteriosus (PDA) is the most prevalent subtype of malformations of the great arteries in this cohort. Isolated cases of PDA are the cases with PDA only.

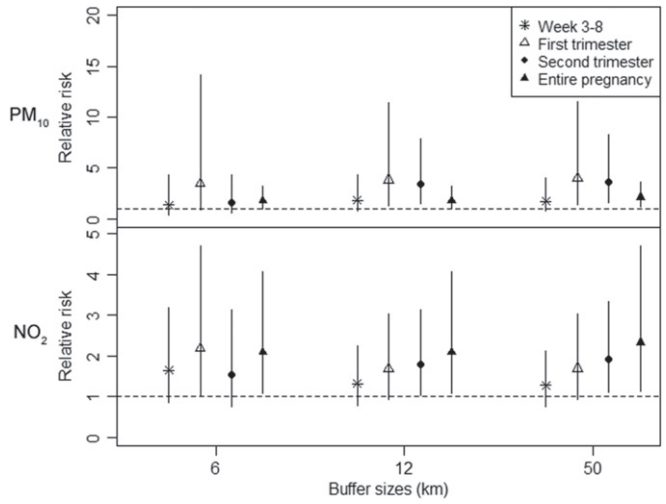

Figure 2. Adjusted ORs (95% CI) for isolated cases of patent ductus arteriosus associated with IQR increases in PM_{10} and NO_2 exposure during each exposure window for women living within 6, 12 and 50 km of a monitor. *Note:* The exposures were estimated using 2 monitors covering the entire period of study.

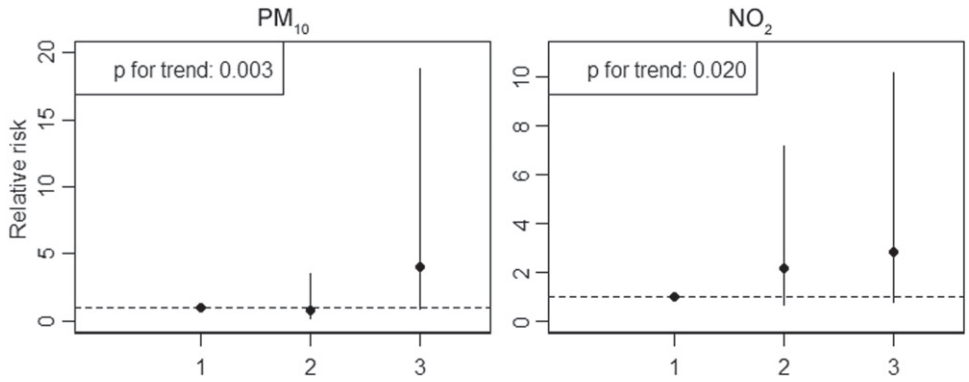

Figure 3. Adjusted ORs (95% CI) for isolated cases of artery defects associated with tertiles of air pollution exposures during the 2nd trimester. *Note:* The point reflects central estimates; vertical lines represent 95% confidence intervals. Estimates represent the risk of congenital heart defects for pollutant exposures in a given tertile compared to the first (lowest) tertile. The exposures were estimated for women living within 50 km of a monitor ($n = 8729$) using 2 monitors covering the entire period of study. The 2nd trimester was chosen because we found the associations in this trimester were stronger for PM_{10} and NO_2 (table 4).

congenital anomalies [29]. However, we did not find positive associations during week 3–8. One possible explanation was that cardiac lesions or defects observed in our cohort were those more likely to be developed in the later stage of fetal development. Although severe and complex cardiac malformations develop during the first 6 to 7 weeks, growing evidence suggests that other defects may occur or progress in utero with advancing gestational age [36–38]. A recent study analyzing scans of the hearts of healthy fetuses found that the heart has distinct left and right chambers by the eighth week of pregnancy, but does not have fully organized muscle tissue until the 20th week [38]. The most prevalent cases in this cohort, PDA, might be related to exposure to air pollution later in pregnancy. Under normal condition, ductus arteriosus constricts immediately after birth so that infant lungs could supply oxygen after the umbilical cord is cut [39]. However, ductus arteriosus could fail to achieve permanent closure due to abnormal levels of agents (e.g., glucocorticoids) regulating the initial contraction of ductal muscle, especially among preterm births [39, 40]. In our cohort, preterm birth was found to be positively associated with higher PM_{10} during the entire and late course of pregnancy [41]. Other prevalent subtypes in our cohort, including VSD and stenosis of the pulmonary artery, might also develop or progress later in pregnancy [36, 37]. Additional research is needed to further investigate the physiological pathways through which air pollution affects birth defects for different types of malformations and timing of exposure during pregnancy. The most relevant exposure timeframe may vary by birth defect, and is challenging to study given correlations

Table 8. Comparisons between this study and previous studies investigating the effects of air pollution exposure on congenital heart defects.

Study location (time period)	Study design (No. of births)	Pollutants studied	Exposure window	Air pollutant exposure estimation methods	Regression models (No. of confounders)	Main results related to congenital heart defects	Study
Lanzhou, China (2009–2012)	Cohort (8969)	PM_{10}, NO_2, SO_2	weeks 3–8; 1st trimester; entire pregnancy	Inverse distance weighting to estimate levels at work and residence. Accounted for residential mobility.	Logistic regression (12)	Significant associations for: PM_{10} exposures during 1st trimester and entire pregnancy and pooled cases; NO_2 exposures during entire pregnancy with pooled cases.	This study
Southern California, US (1987–1993)	Case-control (14 198)	CO, NO_2, O_3, PM_{10}	1st, 2nd, and 3rd month; 2nd and 3rd trimesters; 3-month period prior to conception	Assigned most relevant monitor to each zip code of maternal residence	Logistic regression (10)	Does-response patterns for: 2nd-month CO and ventricular septal defects; 2nd month O_3 exposure and aortic artery and valve defects, pulmonary artery and valve anomalies, and conotruncal defects.	Ritz *et al* (2002)
Texas, US (1997–2000)	Population- based case-control (7381)	CO, NO_2, O_3, PM_{10}	weeks 3–8	Closest monitor	Logistic regression (14)	Significant associations for: CO and tetralogy of Fallot; PM_{10} and isolated atrial septal defects; SO_2 and isolated ventricular septal defects.	Gilboa *et al* (2005)
Georgia, US (1986–2003)	Cohort (715 500)	CO, NO_2, O_3, PM_{10}, SO_2	weeks 3–7	Central monitoring station	Poisson generalized linear models (2)	Significant association for PM_{10} and patent ductus arteriosus.	Strickland *et al* (2009)
Brisbane, Australia (1998–2004)	Case-control (150,308)	CO, NO_2, O_3, PM_{10}, SO_2	weeks 3–8	Closest monitor	Conditional logistic regression (7)	No association between air pollution and cardiac defects.	Hansen *et al* (2009)
Northern Health Region, UK (1985–1990)	Case-control (245 825)	Black smoke, SO_2	1st trimester	Average from monitors within 10 km of residence	Logistic regression (3)	Significant negative association for SO_2 and congenital heart disease.	Rankin *et al* (2009)
Northeast England, UK (1985–1996)	Case-control (12 688)	Black smoke, SO_2	weeks 3–8	Estimation of weekly exposure using 2-stage spatiotemporal model	Logistic regression (5)	Significant association for BS and congenital malformations of cardiac chambers and connections.	Dadvand *et al* (2010)
Northeast England, UK (1993–2003)	Case-control (19 036)	CO, NO_2, O_3, PM_{10}, SO_2, NO	weeks 3–8	Closest monitor to residential postcode	Logistic regression (5)	Significant associations for: CO and NO and ventricular septal defect and cardiac septa malformations; CO and congenital pulmonary valve stenosis; NO and pooled cases.	Dadvand *et al* (2011)
UK (1991–1999)	Case-control (759 993)	NO_2, PM_{10}, SO_2	20 weeks weeks 3–8	Annual mean at census ward level	Poisson regression (3)	Significant association for SO_2 and tetralogy of Fallot.	Dolk *et al* (2009)

Table 8. (Continued.)

Study location (time period)	Study design (No. of births)	Pollutants studied	Exposure window	Air pollutant exposure estimation methods	Regression models (No. of confounders)	Main results related to congenital heart defects	Study
Tel-Aviv region, Israel (2000–2006)	Case-control (135 527)	CO, NO_2, O_3, PM_{10}, $PM_{2.5}$, SO_2		Weekly estimates based on inverse distance weighting	Logistic regression (8)	Significant association for PM_{10} and pooled cases. Significant inverse association for $PM_{2.5}$ and isolated patent ductus arteriosus.	Agay-Shay *et al* (2013)
San Joaquin Valley, CA, US (1997–2006)	Population- based case-control (1,671)	CO, NO, NO_2, PM_{10}, $PM_{2.5}$, O_3	first 2 months	Inverse distance-squared weighting; traffic density indicators representing traffic counts within 300 m of early pregnancy residence. Accounted for residential mobility.	Logistic regression (3)	Significant associations for: PM_{10} with pulmonary valve stenosis and perimembranous ventricular septal defects; $PM_{2.5}$ and transposition of the great arteries; traffic density with muscular ventricular septal defects and perimembranous ventricular septal defects. Inverse associations for: $PM_{2.5}$ and perimembranous ventricular septal defects; CO and secundum atrial septal defects.	Padula *et al* (2013)
Barcelona, Spain (1994–2006)	Case control (5238)	NOx, NO_2, PM_{10}, $PM_{2.5}$, $PM_{10\text{-}2.5}$, $PM_{2.5}$ absorbance	weeks 3–8	Land use regression models.	Logistic regression (4)	Significant association for NO_2 and coarctation of the aorta.	Schembari *et al* (2014)
Nine states, US (1997–2006)	Case control (7960)	CO, NO_2, O_3, SO_2, fine and coarse PM	weeks 2–8	Closet monitor within 50 km to residence	Hierarchical regression (3)	Positive associations for: NO_2 and coarctation of the aorta and pulmonary valve stenosis; fine PM and hypoplastic left heart syndrome. Negative association for fine PM and atrial septal defects.	Stingone *et al* (2014)
Texas (2002–2006)	Population-based case-control (14 23 483)	$PM_{2.5}$, O_3	1st trimester	Hierachical Bayesian model combining data from air monitors with modeled air pollution estimates from CMAQ. Accounted for residential mobility for NBDPS database.	Logistic regression (5)	Significant inverse association for O_3 and septal heart defects.	Vinikoor-Imler *et al* (2015)

among exposures. For example, in this study exposure in week 3–8 and the first trimester were highly correlated (table 2), although results were somewhat different (table 4).

To our knowledge, this is the first study investigating the associations of air pollution with congenital heart defects in Asia. One advantage of this study is the detailed residential history, work address, and lifestyle choices reported by the women. Most studies of air pollution and pregnancy outcomes estimate exposure based on residence at time of birth, which introduces exposure misclassification as women move during pregnancy [1, 42, 43]. Residential mobility was only considered in one previous study on congenital heart defects and air pollution, which did not report the improvement due to incorporating residential mobility [14]. The percentage of women who moved during pregnancy in our study is 3.1%, which is lower than the ~30% reported in the western World [2]. Considering residential mobility might not have significant influence on the exposure estimation in this study. This is the first study considering maternal exposures at work locations on this topic. In general, central effect sizes for PM_{10} and NO_2 estimated only using exposures at home were slightly smaller than using exposures at both home and work. However, in general the 95% CI are reduced slightly when considering the home address only. Although we incorporated exposure at work locations in the exposure assessment, in an attempt to improve the exposure estimate, the actual exposure is based on time at work, home, shopping, etc. Berkson error in the assessment of exposure (i.e. error that is statistically independent from the observed variable) can occur if our exposure estimates include part of the true exposure, whereas classical measurement error includes the true exposure as well as noise [44]. Berkson error typically results in an unbiased but more variable health effect estimates, whereas classical error can result in biased estimates with incorrect estimates of standard error [45]. Additional research is needed to better understand potential sources of exposure misclassification and their impacts on results. For example, we did not account for exposure during commuting and our study lacks information on activity patterns. The linear distance between home and work averaged 7.5 km (IQR: 6.6 km). There was no significant difference in the distance from home to work between infants with and without congenital heart defects (p-value: 0.82). Therefore, misclassification due to time spent commuting might have a minimal impact on results. Future studies could investigate other factors influencing maternal exposures during commuting, such as means of transportation.

This is also the first study to control for therapeutic drug intake during pregnancy, a known risk factor for congenital heart defects [31]. Other confounders, including maternal folic acid intake, illness, smoking and household cooking fuel, were also seldom considered in previous studies. The percentage of women smoking during pregnancy in Lanzhou (20%) did not differ significantly between infants with and without congenital heart defects. This is consistent with previous studies in the US, which reported comparable or smaller percentage of women smoking (<19%) [12, 14, 18, 20]. However, one study in Barcelona reported a higher percentage of women smoking during pregnancy (42%) and found positive associations for smoking with pooled cases [17].

On the other hand, the accuracy of exposure estimation might be limited by the lack of monitors in rural areas in Lanzhou city. However, more than 95% of the women lived within 10km of a monitor. Sensitivity analysis using the data from all 4 monitors and women living within 6 or 12 km of a monitor all showed consistent results. Compared to some previous studies, the sample size in our study was smaller, which might lead to a less statistical power, although the detail provided by the cohort study allows better exposure estimation and adjustment of covariates. Another limitation is the lack of information on congenital anomalies for termination of pregnancies.

Studies with data from more monitoring stations and more types of air pollutants are needed to fully understand the impacts of the air pollution mixture on congenital heart defects in China, and such studies may be possible as the air pollution monitoring system has become more extensive in China since 2013. Future studies in Asia and elsewhere should analyze the subtypes of congenital heart defects because they are anatomically, clinically and epidemiologically heterogeneous [46].

In summary, we found significant associations between gestational exposures to PM_{10} and NO_2 and congenital heart defects risk after controlling for demographic variables, maternal health status and maternal lifestyle choices. This present study is the first on this issue conducted in Asia, where air pollution levels and prevalence of congenital heart defects are both high. These findings contribute to the modest body of scientific literature regarding the impacts of air pollution on birth defects.

Acknowledgments

This work was supported by internal funding from the Gansu Provincial Maternity and Child Care Hospital; Gansu Provincial Science and Technology Department Grant [1204WCGA021]; and the National Institutes of Health [K02HD70324, R01ES019587]. We thank all the study personnel from the Gansu Provincial Maternity and Child Care Hospital for their exceptional efforts on study subject recruitment, and Dr Joshua Warren of Yale University.

References

[1] Vrijheid M *et al* 2011 Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis *Environ. Health Perspect.* **119** 598–606

[2] Polichetti G *et al* 2013 Effects of ambient air pollution on birth outcomes: an overview *Crit. Rev. Environ. Sci. Technol.* **43** 1223–45

[3] Sram R J *et al* 2005 Ambient air pollution and pregnancy outcomes: a review of the literature *Environ. Health Perspect.* **113** 375–82

[4] Glinianaia S V *et al* 2004 Particulate air pollution and fetal health a systematic review of the epidemiologic evidence *Epidemiology* **15** 36–45

[5] Maisonet M *et al* 2004 A review of the literature on the effects of ambient air pollution on fetal growth *Environ. Res.* **95** 106–15

[6] Mathews T J and MacDorman M F 2011 Infant mortality statistics from the 2007 period linked birth/infant death data set *Natl. Vital. Stat. Rep.* **59** 1–30

[7] van der Linde D *et al* 2011 Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis *J. Am. Coll. Cardiol.* **58** 2241–7

[8] Agay-Shay K *et al* 2013 Air pollution and congenital heart defects *Environ. Res.* **124** 28–34

[9] Dadvand P *et al* 2011 Ambient air pollution and congenital heart disease: a register-based study *Environ. Res.* **111** 435–41

[10] Dadvand P *et al* 2011 Association between maternal exposure to ambient air pollution and congenital heart disease: a register-based spatiotemporal analysis *Am. J. Epidemiol.* **173** 171–82

[11] Dolk H *et al* 2010 Ambient air pollution and risk of congenital anomalies in England, 1991-1999 *Occup. Environ. Med.* **67** 223–7

[12] Gilboa S M *et al* 2005 Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000 *Am. J. Epidemiology* **162** 238–52

[13] Hansen C A *et al* 2009 Ambient air pollution and birth defects in Brisbane, Australia *Plos One* **4** e5408

[14] Padula A M *et al* 2013 Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin Valley of California *Paediatric and Perinatal Epidemiol.* **27** 329–39

[15] Rankin J *et al* 2009 Maternal exposure to ambient air pollutants and risk of congenital anomalies *Environ. Res.* **109** 181–7

[16] Ritz B *et al* 2002 Ambient air pollution and risk of birth defects in southern California *Am. J. Epidemiol.* **155** 17–25

[17] Schembari A *et al* 2014 Traffic-related air pollution and congenital anomalies in barcelona *Environ. Health Perspect.* **122** 317–23

[18] Stingone J A *et al* 2014 Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the national birth defects prevention study *Environ. Health Perspect.* **122** 863–72

[19] Strickland M J *et al* 2009 Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986–2003 *Am. J. Epidemiol.* **169** 1004–14

[20] Vinikoor-Imler L C *et al* 2015 An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas *Environ. Pollut.* **202** 1–6

[21] WHO 2011 *Database: outdoor air pollution in cities* (www.who.int/phe/health_topics/outdoorair/databases/cities-2011/en/)

[22] Ta W *et al* 2004 Gaseous and particulate air pollution in the Lanzhou Valley, China *Sci. Total Environ.* **320** 163–76

[23] Ministry of Environmental Protection of the People's Republic of China 2012 *Ambient Air Quality Standards* GB 3095-2012 (http://kjs.mep.gov.cn/hjbhbz/bzwb/dqhjbh/dqhjzlbz/201203/t20120302_224165.htm)

[24] U.S. Environmental Protection Agency 2012 *National Ambient Air Quality Standards* [NO2: Feb 9, 2010; PM10: Dec 14, 2012; SO2: Jun 22, 2010] (www.epa.gov/air/criteria.html)

[25] WHO 2006 *Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide, and Sulfur Dioxide* (Geneva: WHO)

[26] Zhang Y *et al* 2014 Air quality in Lanzhou, a major industrial city in China: characteristics of air pollution and review of existing evidence on air pollution and health studies *Water, Air, & Soil Pollution* **225** 1–17

[27] Qiu J *et al* 2014 Passive smoking and preterm birth in urban China *Am. J. Epidemiol.* **180** 94–102

[28] Opitz J M and Clark E B 2000 Heart development: an introduction *Am. J. Med. Genet.* **97** 238–47

[29] Kim O J *et al* 2007 PM10 and pregnancy outcomes: a hospital-based cohort study of pregnant women in Seoul *J. Occup. Environ. Med.* **49** 1394–402

[30] Barba C *et al* 2004 Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies *Lancet* **363** 157–63

[31] Jenkins K J *et al* 2007 Noninherited risk factors and congenital cardiovascular defects: current knowledge a scientific statement from the American Heart Association Council on cardiovascular disease in the young *Circulation* **115** 2995–3014

[32] Thomson Reuters 2015 *Web of Science* (http://apps.webofknowledge.com/)

[33] Medicine USNLo 2015 *PubMed Health* (www.ncbi.nlm.nih.gov/pubmedhealth/)

[34] SciVerse 2015 *Scopus* (www.scopus.com/home.url)

[35] Liu X Q *et al* 2013 Current prevalence rate of congenital heart disease in 12 month-old and younger infants among four regions of Guangdong province *Zhonghua Xin Xue Guan Bing Za Zhi* **41** 337–40

[36] Trines J and Hornberger L K 2004 Evolution of heart disease in utero *Pediatr. Cardiol.* **25** 287–98

[37] Yagel S *et al* 1997 Congenital heart defects: natural course and in utero development *Circulation* **96** 550–5

[38] Pervolaraki E *et al* 2013 Antenatal architecture and activity of the human heart *Interface Focus* **3** 20120065

[39] Coceani F and Baragatti B 2012 Mechanisms for ductus arteriosus closure *Semin. Perinatol.* **36** 92–7

[40] Clyman R I *et al* 1999 Permanent anatomic closure of the ductus arteriosus in newborn baboons: the roles of postnatal constriction, hypoxia, and gestation *Pediatr. Res.* **45** 19–29

[41] Zhao N *et al* 2015 Ambient air pollutant PM10 and risk of preterm birth in Lanzhou, China *Environ. Int.* **76** 71–7

[42] Bell M L and Belanger K 2012 Review of research on residential mobility during pregnancy: consequences for assessment of prenatal environmental exposures *J. Expo. Sci. Environ. Epidemiol.* **22** 429–38

[43] Slama R *et al* 2008 Meeting report: atmospheric pollution and human reproduction *Environ. Health Perspect.* **116** 791–8

[44] Sheppard L *et al* 2005 Exposure and measurement contributions to estimates of acute air pollution effects *J. Exposure Anal. Environ. Epidemiol.* **15** 366–76

[45] Sheppard L *et al* 2012 Confounding and exposure measurement error in air pollution epidemiology *Air Qual. Atmos. Health* **5** 203–16

[46] Botto L D *et al* 2007 Seeking causes: classifying and evaluating congenital heart defects in etiologic studies *Birth Defects Res. A Clin. Mol. Teratol* **79** 714–27