Journal of Exposure Science and Environmental Epidemiology (2016) 26, 422–427

www.nature.com/jes

OPEN

ORIGINAL ARTICLE

Maternal exposure to air pollutant $PM_{2.5}$ and PM_{10} during pregnancy and risk of congenital heart defects

Bin Zhang[1,6], Shengwen Liang[2,6], Jinzhu Zhao[1,6], Zhengmin Qian[3], Bryan A. Bassig[4], Rong Yang[1], Yiming Zhang[1], Ke Hu[2], Shunqing Xu[5], Tongzhang Zheng[4] and Shaoping Yang[1]

Maternal exposure to ambient air pollution has increasingly been linked to congenital heart defects (CHDs). The objective of this study was to evaluate whether high levels of maternal exposure to $PM_{2.5}$ and PM_{10} are related to increased risk of CHDs in Wuhan, China. We conducted a cohort study with a total of 105,988 live-born infants, stillbirths, and fetal deaths. The study included mothers living in the urban district of Wuhan during pregnancy over the 2-year period from 10 June 2011 to 9 June 2013. For each study participant, we assigned 1-month and 1-week averages of PM_{10} and $PM_{2.5}$ exposure based on measurements obtained from the nearest exposure monitor to the living residence of mothers during their early pregnancy period. Logistic regression analyses were conducted to calculate the adjusted odds ratios (aORs) and 95% confidence intervals (CI) for the association between exposure to these ambient air pollutants during early pregnancy and CHDs. We observed an increased risk of CHDs, particularly ventricular septal defect (VSD), with increasing $PM_{2.5}$ exposure. Using 1-week averages, we also observed significant monotonically increasing associations between $PM_{2.5}$ exposure during weeks 7–10 of pregnancy and risk of VSD, with aORs ranging from 1.11 to 1.17 (95% CI: 1.02–1.20, 1.03–1.22, 1.05–1.24, and 1.08–1.26 separately) per a 10 $\mu g/m^3$ change in $PM_{2.5}$ concentration. Our study contributes to the small body of knowledge regarding the association between *in utero* exposure to air pollution and CHDs, but confirmation of these associations will be needed in future studies.

Journal of Exposure Science and Environmental Epidemiology (2016) **26,** 422–427; doi:10.1038/jes.2016.1; published online 17 February 2016

Keywords: air pollution; congenital heart defects; $PM_{2.5}$; PM_{10}

INTRODUCTION

Congenital anomalies are recognized to be major causes of infant mortality and leading causes of disability. Worldwide, 3.2 million disabilities every year[1] and 10% of deaths in children <5 years old are caused by congenital anomalies.[2,3] In the United States, ~3% of births are associated with a birth defect.[4] In China, the incidence of congenital malformations is 5.6%, with ~900,000 new birth defect cases each year.[5] Congenital heart defects (CHDs), which accounted for 27% of all birth defects in China in 2011, are the most common severe congenital anomalies and are the leading causes of infant mortality in China (Report MoHoPs-RoCCBDP). A recent report showed a rapid increase in CHDs in China during 1996–2011.[6] The precise etiology of most congenital anomalies is not fully understood, and is suggested to have multifactorial causes, including environmental exposures.[7]

Although many epidemiological studies have investigated the relationship between maternal exposure to ambient air pollutants during pregnancy and risk of preterm delivery (PTD), low birth weight (LBW), and infant mortality,[8–11] few studies have investigated the association between maternal air pollution exposure and risk of congenital anomalies.[12–14] Animal studies have suggested that *in utero* exposure to air pollutants could induce teratogenic effects in the fetus.[7,15] Further, the existing literature indicates that the effects of particulate matter (PM) on LBW, PTD, and intrauterine growth restriction (IUGR) may manifest through cardiovascular mechanisms involving oxidative stress, inflammation, coagulation, endothelial function, and hemodynamic responses,[16,17] which provides biological rationale for the evaluation of the relationship between exposure to air pollution and CHDs. Several studies have reported an increased risk of pulmonary valve stenosis, perimembranous ventricular septal defect (VSD),[18] multiple CHDs,[7] atrial septal defects,[19] and patent ductus arteriosus[20] in relation to ambient PM_{10} exposure, and an increased risk of dextro-transposition of the great arteries[18] in relation to ambient $PM_{2.5}$ exposure.

The evidence for an impact of PM on congenital anomaly risk is still limited.[3,12] A meta-analysis that combined the results from four individual studies reported that NO_2 was significantly associated with the risk of coarctation of the aorta.[3] Another meta-analysis that combined results from four studies reported that NO_2 and SO_2 were related to increased risk of coarctation of the aorta and Tetralogy of Fallot (TF), and PM_{10} was related to increased risk of atrial septal defects.[12] However, $PM_{2.5}$ was not assessed in either of these meta-analyses and a limited

[1]Guidance Department for General Staff, Wuhan Women and Children Health Care Center, Wuhan, Hubei Province, China; [2]Wuhan Environmental Monitoring Center, Wuhan, Hubei Province, China; [3]Department of Epidemiology, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri, USA; [4]Department of Environmental Health Sciences, Yale University School of Public Health, New Haven, Connecticut, USA and [5]Key Laboratory of Environment and Health, Ministry of Education & Ministry of Environmental Protection, and State Key Laboratory of Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China. Correspondence: Tongzhang Zheng, Department of Environmental Health Sciences, Yale University School of Public Health, 60 College Street, New Haven, CT 06510, USA or Shaoping Yang, Wuhan Women and Children Health Care Center, Hongkong Road 100, Wuhan, Hubei Province 430030, China.
Tel.: +1 203 785 2882 or +86 027 82433 244. Fax: +86 027 82433 492.
E-mail: tongzhang.zheng@yale.edu or mchwhzb@163.com
[6]Co-first author.
Received 17 February 2015; accepted 28 November 2015; published online 17 February 2016

Figure 1. The study area and the distribution of monitoring stations of Wuhan city.

number of specific congenital anomalies were evaluated in prior epidemiological studies. In addition, most previous studies assigned exposure using daily pollutant averages over weeks 3–8 after conception. This method did not consider temporal variability in exposure across specific windows within cardiac development. Moreover, most prior studies have been conducted in developed countries, which may have lower pollution levels and narrow pollution ranges. In contrast, very few studies have been conducted in developing countries where air pollution is more severe, and consequently the association between ambient air pollution and congenital heart anomalies at very high levels of pollution is still unclear.

Unprecedented economic development in China over past several decades has contributed to severe air pollution in Chinese cities and increasing public health concern about the effects of these exposures. Here, we report the results from a study of exposure to PM_{10} and $PM_{2.5}$ during the first trimester of pregnancy and the risk of CHDs involving 105,988 births in Wuhan, one of the most polluted cities in China.

METHODS

Study Population

This study used a population-based cohort design. The cohort population consisted of births from a perinatal health-care system for women and children of Wuhan, which has accrued approximately 100,000 births/year from nearly all maternity units in Wuhan city (including urban and rural area) since its start in 2003. The perinatal health-care system is a standardized, computer-based database including information on demographic characteristics, medical history, prenatal examinations, deliveries, and postnatal visits for mothers and infants. Births enrolled in our study included live-born infants, stillbirths, and fetal deaths (gestational age ≥ 20 weeks). The study only included mothers living in the urban district of Wuhan during pregnancy over the 2-year period from 10 June 2011 to 9 June 2013.

A total of 108,167 births were enrolled initially. Of these, 911 were excluded because of the presence of other malformations in other organ systems not involving the heart, and 1280 births were excluded because of incomplete demographic information. A total of 105,988 births met the study inclusion criteria, and of these 188 infants were diagnosed with CHDs. Cases for this study were defined as those infants with a CHD based on confirmation from clinical, surgical, or autopsy reports. Cases included live births, stillbirths after 20 weeks of gestation, as well as pregnancies that were terminated following a prenatal diagnosis of either isolated or multiple CHDs. Cases with chromosomal anomalies or those with identifiable syndromes were ineligible for the study. Cases were classified into anomaly subgroups according to the International Classification of Diseases, 10th Revision (ICD-10). We evaluated all CHDs combined (Q20-Q28) and the two most common subgroups of cardiac anomalies individually, namely VSD (Q21.0) and TF (Q21.3).

The study protocol was reviewed and approved by the Health Department of Hubei Province and the Institutional Review Board at the Wuhan Women and Children Health Care Center.

Maternal Exposure Assessment for PM_{10} and $PM_{2.5}$

There were nine national ambient air quality automatic monitoring stations that were operational during 2011–2013 across the study region. These monitoring stations were located in the urban districts of Wuhan with a relatively uniform distribution. The installation of air quality monitoring stations was in strict accordance with the "monitoring rules on environmental air quality in China".[21] The monitoring stations provide 24-h measurements of PM_{10} and $PM_{2.5}$. During the study period there were nine monitors measuring PM_{10}, and two monitors measuring $PM_{2.5}$. We restricted our population to those pregnancies with measurement data available on ≥ 1 days of each week, and ≥ 10 days of each month of the first trimester. For $PM_{2.5}$ and PM_{10}, 89% and 99.9% of the original study population met this criterion, respectively. The data for these measurements were obtained from Wuhan Environmental Monitoring Center.

The exposure assessment was performed for the first 3 months of pregnancy, and we averaged the 24-h measurements for the first 3 months of pregnancy. We also assigned 1-month and 1-week averages of the daily values for PM_{10} and $PM_{2.5}$ for each study participant.

We used the closest monitor approach and took the following steps to assign air pollution exposures to each mother. For PM_{10}, we first obtained the latitude and longitude of each station and calculated the perpendicular bisector of any two monitor stations. Eighteen perpendicular bisectors

Table 1. Characteristics of the study subjects.

Item	*Infants without any malformations (N = 105,800)*	*CHDs (N = 188)*	P-*value*
Maternal age (years)			0.518
< 20	19,813 (18.73)	29 (15.43)	
20–25	53,060 (50.15)	102 (54.26)	
25–30	25,237 (23.85)	46 (24.47)	
> 35	7690 (7.27)	11 (5.85)	
Maternal education (years)			0.756
< 12	15,578 (14.76)	31 (16.49)	
12–15	45,917 (43.51)	78 (41.49)	
> 15	44,042 (41.73)	79 (42.02)	
Missing	263		
Parity			0.9854
1	81,098 (76.65)	144 (76.60)	
> 1	24,702 (23.35)	44 (23.40)	
Infant sex			0.8196
Male	56,355 (53.27)	97 (52.43)	
Female	49,437 (46.73)	88 (47.57)	

Abbreviation: CHD, congenital heart defect.

Table 2. Adjusted[a] odds ratios and 95% CI for CHDs and exposure to $PM_{2.5}$ and PM_{10} during the first 3 months of pregnancy.

	All congenital heart defects (Q20-Q28) (N = 188)	*Ventricular septal defect (Q21.0) (N = 63)*	*Tetralogy of Fallot (Q21.3) (N = 29)*
	aOR (95% CI)	*aOR (95% CI)*	*aOR (95% CI)*
$PM_{2.5}$			
First M[b]	1.01 (0.93–1.09)	1.11 (0.98–1.25)	1.05 (0.89–1.26)
Second M[c]	1.10 (1.03–1.18)	1.16 (1.03–1.30)	1.13 (0.96–1.32)
Third M[d]	1.08 (1.01–1.16)	1.21 (1.08–1.36)	1.03 (0.87–1.22)
PM_{10}			
First M[b]	0.94 (0.89–1.01)	0.97 (0.87–1.09)	0.84 (0.71–1.01)
Second M[c]	0.99 (0.92–1.05)	0.96 (0.86–1.07)	0.99 (0.84–1.17)
Third M[d]	0.98 (0.93–1.05)	0.99 (0.90–1.10)	1.00 (0.85–1.17)

Abbreviations: aORs, adjusted odds ratio; CHD, congenital heart defect; CI, confidence interval. [a]Adjusted for maternal age, education, parity, infant sex, and season of conception. [b]First M: the first month exposure. [c]Second M: the second month exposure. [d]Third M: the third month exposure.

divided the central districts of Wuhan into nine areas (Figure 1). Each area had one monitoring station that was the closest station to every residence in the area, which can be proved by law of sines.[22] Second, each maternal residence was assigned manually to these nine areas according to their residential communities. There were a total of 98 communities, and the average area of the communities is ~2 km^2 (Figure 1). For large communities, which may cover two or more areas, we chose the closest monitor that most of the community relied on. Third, we assigned an estimate for each air pollutant on each day of gestation using the closest monitoring station to the community of interest. These same procedures were conducted for the $PM_{2.5}$ exposure assessment, except that the districts of Wuhan were divided into two areas rather than nine based on the two PM2.5 monitoring stations that were in operation.

Potential Confounders

Other variables extracted from the database that were adjusted for included maternal age (< 25, 25–35, and > 35 years), education (< 12, 12, 13–15, > 15 years), parity (1, > 1), infant sex (male/female), and season of conception (Spring: March–May; Summer: June–August; Fall: September–November; and Winter: December–February). These covariates were selected based on evidence for their association with CHDs in previous studies. We also considered adjusting for maternal smoking and maternal alcohol consumption, but the prevalence of these characteristics was low in the study population (< 0.7% and < 0.5%, respectively).

Statistical Methods

We used multivariable logistic regression analyses to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CI) for the association between ambient air pollutants and CHDs. AORs and 95% CIs were calculated for CHDs overall and individually for VSD and TF. Evaluation of other individual defects was not possible because of the small sample sizes. We also evaluated the relationship between exposure levels in each week of pregnancy (up to 12 weeks) and these congenital defects because of uncertainty of the specific windows of susceptibility and the lack of clearly elucidated mechanisms by which cardiac development could be disrupted by exposure to air pollution.[23] If a woman did not have at least one monitoring value for each week of exposure, she was excluded from this analysis. A total of 87,975 women had weekly exposure data and were included in this analysis. We present the effect of each pollutant on the risk of CHDs as aORs per a 10-$\mu g/m^3$ change for PM_{10} and $PM_{2.5}$, along with their 95% CIs. To evaluate the associations between $PM_{2.5}$ and CHD, PM_{10} and CHD in other periods of pregnancy, we conducted a sensitivity analyze that included first, second and third trimester exposures of pregnancy. To evaluate the effect of the distance between the maternal residences and the $PM_{2.5}$ monitoring stations on the observed associations, we draw 10 km radius from the monitor stations measuring $PM_{2.5}$ (see Supplementary Material, Figure S1), and conducted sensitivity analyses that excluded women who lived > 10 km from a monitoring station. We used the same procedures of exposure assessment for 105,988 subjects to exclude women living > 10 km from a monitoring station, and this performed based on the locations of subjects' residential communities.

Analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA) and $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Subjects

Table 1 shows descriptive statistics of the birth cohort. There were 105,988 births during the study period that met the study inclusion criteria. The prevalence rate of CHD was 17.7 per 10,000, with the highest rate observed for VSD (6.2 per 10,000) followed by TF (2.7 per 10,000). The majority of the cohort members had a maternal age < 25 years at delivery (69%), and had at least a high school education (85%). For ~80% of women, this was their first pregnancy and first-born child because of a one-child policy in China. There were no statistically significant differences between infants with CHDs and infants without malformations for maternal age, maternal education, parity, or infant sex.

Air Pollution and the Risk of CHDs

The mean (25th–75th percentile range) of the exposure concentrations of the air pollutants was 65.61 $\mu g/m^3$ (37.80–85.04 $\mu g/m^3$) for PM2.5 and 101.73 $\mu g/m^3$ (59.17–134.00 $\mu g/m^3$) for PM10.

Table 2 shows the aORs and 95% CIs for the risk of CHDs in relation to $PM_{2.5}$ and PM_{10} exposure by each month of the first trimester of pregnancy. We observed a positive association between all CHDs and $PM_{2.5}$ particularly in the second month of pregnancy (adjusted OR = 1.10 per 10 $\mu g/m^3$ change; 95% CI: 1.03–1.18), and third month of pregnancy (adjusted OR = 1.08; 95% CI: 1.01–1.16). The effect estimate for $PM_{2.5}$ exposure during the first month of pregnancy was not statistically significant (adjusted OR = 1.01; 95% CI: 0.93–1.09). We also observed that the risk of VSD associated with exposure to $PM_{2.5}$ increased gradually as the month increased. Specifically, the adjusted OR for a 10-$\mu g/m^3$ change in $PM_{2.5}$ was 1.11 (95% CI: 0.98–1.25) for the first month of pregnancy, 1.16 (95% CI: 1.03–1.30) for the second month of pregnancy, and 1.21 (95% CI: 1.08–1.36) for the

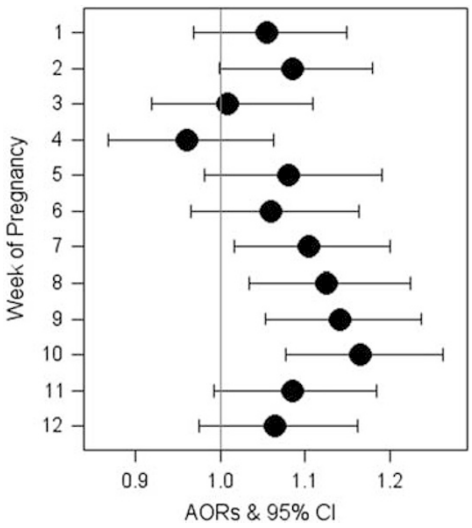

Figure 2. Estimated adjusted ORs and 95% CIs of Ventricular septal defect for continuous measures of 1-week averages of daily measures of PM2.5, plotted for weeks 1–12 pregnancy. CI, confidence interval; OR, odds ratio.

third month of pregnancy. But 95% CI overlap between the 3 months was large, and suggested there could be no increase by month. No significant associations were observed between $PM_{2.5}$ exposure and TF. Similarly, there were no significant associations between PM_{10} exposure and CHDs overall or for VSD and TF individually.

We also detected an increased risk of all CHDs in relation to higher $PM_{2.5}$ exposure during the second month, and an increased risk of VSD for higher $PM_{2.5}$ exposure during the third month when the study participants living further than 10 km from a monitoring station were excluded from the analysis (see Supplementary Material, Table S1).

Figure 2 shows the estimated aORs and 95% CIs for the weekly exposure analyses in relation to risk of VSD (see Supplementary Material, Table S2, for corresponding numerical data). Risk of VSD showed variability across the first 12 weeks of pregnancy and the results suggested that $PM_{2.5}$ exposures after the first 6 weeks, particularly during weeks 7–10, may be associated with a greater susceptibility to developing VSD. Specifically, the estimated risks of VSD for $PM_{2.5}$ exposures during weeks 1–6 of pregnancy were generally slightly elevated but not statistically significant. During weeks 7–10 (5th week to 8th week after fertilization), the estimated risk of VSD in relation to $PM_{2.5}$ exposure gradually increased, with aORs for VSD ranging from 1.11 to 1.17. In weeks 11 and 12, the estimated risk was also increased slightly, but not as high as in weeks 7–10.

We only detected an increased risk of all CHDs in relation to higher $PM_{2.5}$ exposure during the second trimester and VSD in relation to higher $PM_{2.5}$ exposure during the third trimester in sensitivity analysis. The association between all CHDs and $PM_{2.5}$ exposure during the third trimester, VSD and $PM_{2.5}$ exposure during the second trimester changed from a large increase in risk to a small increase, which is close to null when we compared exposures during other periods of pregnancy (see Supplementary Material, Table S3).

DISCUSSION

During the past few decades, CHDs are the leading cause of infant mortality due to congenital anomalies, and the aetiologies are unknown for the majority of these defects.[24] Recent studies conducted in developed countries have found some associations between PM exposure and particular CHDs.[7,18–20] However, the evidence for the association between PM and congenital anomalies is still weak.

In this large cohort study conducted among Chinese women and infants exposed to a very high level of pollution, we observed an increased risk of CHDs, particularly VSD, with increasing $PM_{2.5}$ exposure. Using 1-week averages, we also observed monotonically increasing associations between $PM_{2.5}$ exposure during weeks 7–10 of pregnancy and risk of VSD. Our results provide evidence that $PM_{2.5}$ exposure during pregnancy may increase the risk of CHDs.

Possibly because of the higher level of $PM_{2.5}$ pollution in Wuhan, a monotonically increasing the association between $PM_{2.5}$ exposure and VSD was noted in weeks 7–10 in our study, which suggested there may be cumulative effect of risk within the window of cardiac development. And after weeks 10 in our study, a decrease between $PM_{2.5}$ exposure and VSD was found, which assumed it is because the susceptibility window is over. Embryological evidence indicates that cardiac development begins with the migration of cells, including neural crest cells and epicardium-derived cells, to form the endocardial tubes and culminating with the septation of the ventricles and outflow tracts.[23,25] Experimental research has showed that oxidative stress can affect organogenesis and neural crest cell migration and differentiation.[26] This suggests that oxidative stress induced by air pollution during pregnancy[17] in earlier weeks may have an effect on cardiac development, and the risk may increase as the exposure time increases; however, the susceptibility windows for these adverse effects arising from environmental insults may not directly coincide with the established stages of fetal heart development.[23]

Some other studies also found that there may be particular exposure periods within the window of cardiac development that are associated with greater susceptibility to cardiac defects. A study conducted in Texas used weekly averages of $PM_{2.5}$ exposure and found that exposures during weeks 3, 7, and 8 of the pregnancy were particularly associated with the risk of cardiac defect development.[19] The National Birth Defects Prevention Study conducted in the United States also found that exposure to air pollutants during weeks 2, 3, and 5 of pregnancy were associated with risk of pulmonary valve stenosis (PVS).[23] Further studies are still needed to explore how timing of exposure within this narrow window may affect the risk of CHDs.

Most previous studies assigned exposure by averaging daily pollutant averages over the critical window (weeks 3–8).[7,18,26–29] This method does not capture the temporal variability in exposure within the windows of cardiac development. For example, the U.S study observed that $PM_{2.5}$ exposure during week 5 of pregnancy was associated with PVS. However, no associations were observed when they used a summary measure of exposure of summary week average.[23] One explanation for this masking or attenuating associations is that the timing of the environmental insult for certain heart defects is very precise and narrow,[28] so methods relying on summary measures as used in previous studies may not be sensitive enough to detect the associations. In this study, we separated a single overall average into weekly averages to fully reflect the specific windows of susceptibility, and found that exposures to $PM_{2.5}$ during weeks 7 to 10 of pregnancy were particularly important for VSD development.

Some studies have found a positive association between $PM_{2.5}$ exposure and LBW, IUGR, and PTD.[30] However, epidemiological evidence linking maternal $PM_{2.5}$ exposure to CHDs is still limited and inconsistent. The California study estimated the odds of CHDs with respect to quartiles of ambient air pollutants and traffic exposures during the first 2 months of pregnancy and reported positive associations between $PM_{2.5}$ and transposition of the great arteries, but inverse associations between $PM_{2.5}$ and PVS.[18] The U.S study conducted in nine states used daily maximum

pollutant levels during weeks 2–8 after conception and reported that exposure to $PM_{2.5}$ was positively associated with hypoplastic left heart syndrome but inversely associated with atrial septal defects.[23] Inverse associations have also been observed in other studies. The Barcelona study[26] observed decreased ORs between $PM_{2.5}$ exposure during weeks 3–8 of pregnancy and VSD based on a spatiotemporal model. The North Carolina study[27] observed inverse associations between atrial septal defects and $PM_{2.5}$ exposure during weeks 3 to 8 after conception. And a study conducted in Israel observed an inverse association between $PM_{2.5}$ exposure during 3–8 weeks after conception and isolated patent ductus arteriosus.[7] Other cardiac defects examined in these five studies did not demonstrate an association with $PM_{2.5}$ concentration.

These inverse associations between $PM_{2.5}$ exposure and CHDs might be indicative of methodological limitations as well as unknown confounding factors, but they also might be explained partially by the hypothesis that environmental insults may affect the survival of affected fetuses.[29,31] Ritz et al.,[32] for example, have suggested that the inverse association between CO exposure during pregnancy and chromosomal abnormalities might be explained by the increased vulnerability caused by CO and the resulting increased proportion of early spontaneous abortions, which in turn could contribute to an observed inverse association in epidemiological studies.

Particulate levels in our study were higher compared with those in previous studies. The mean $PM_{2.5}$ concentration in Wuhan during the study period was 65.61 $\mu g/m^3$ with a 25th to 75th percentile range from 37.80–85.04 $\mu g/m^3$. Only 12% of the daily $PM_{2.5}$ concentrations in our study achieved the WHO Air Quality Guidelines target (25 $\mu g/m^3$). In the previous studies, the mean levels of $PM_{2.5}$ exposure were 26.1 ug/m^3 in Israel,[7] 16.6 ug/m^3 in Barcelona,[20] and 20.01 ug/m^3 in California.[18] Thus, the inconsistent associations across studies may be related to the differences in $PM_{2.5}$ exposure levels in the study populations. Our study provides evidence that extremely high exposures to $PM_{2.5}$ may be needed to detect associations between PM exposure and CHDs.

Additionally, the inconsistent associations may also be due to different exposure classification. The exposure assessment in previous studies of CHDs and air pollution has been conducted generally using three approaches. These include pure temporal approaches,[20] pure spatial modeling,[14] or using the nearest monitor approach.[19] Some studies have used cruder spatial surrogates than residence such as zip code or a similar area measure,[28,32] which may result in misclassification and compromise the ability to detect true associations between air pollutants and CHDs. Finally, some studies have used spatiotemporal modeling and found that the exposure variation increased after the temporal adjustment,[26] but less refined spatial resolution was used to assess the exposure,[7,18] which could be a source of exposure misclassification. We classified maternal exposure to ambient air pollutants by assigning each mother to the nearest air pollution monitor in our study. Another exposure misclassification is that we estimated exposures based on residential communities, rather than the distance from the monitor station to each maternal address during the study period, thus we not address spatial heterogeneity of pollutants. Additionally, we conducted sensitivity analyses and observed the attenuation of the results when limiting to those women living < 10 km from a monitoring station. Possible misclassification may occur. This misclassification is more likely to be non-differential and would occur approximately equally between study groups (exposed *vs* unexposed), thus increasing the similarity of study groups and making the relative risk for any true exposure-disease association biased towards the null.

Maternal PM_{10} exposure was not associated with CHDs in our study. These results are similar to other studies that have explored the associations between PM_{10} and CHDs. Studies conducted in southern California,[32] England,[13,14] Australia,[27] Barcelona,[25] and nine U.S states[22] reported no association between PM_{10} concentration and cardiac defects. However, some studies have reported associations between PM_{10} and specific outcomes including PVS and perimembranous VSD,[18] patent ductus arteriosus,[20] and atrial septal defects.[19] Other subtypes of CHDs examined in these three studies did not show an association with PM_{10}. In a meta-analysis of ambient air pollution and risk of congenital anomalies, PM_{10} exposure was associated with an increased risk of atrial septal defects,[12] which was not examined in our study because of the small sample sizes. The inconsistencies of the current results are also not easily explained given strong heterogeneity in study designs, study populations, and methodological approaches.[33,34] Biologically, it is possible that associations with $PM_{2.5}$ but not PM_{10} could be at least partially due to larger particles (e.g., PM_{10}) demonstrating a greater fractional deposition in the extrathoracic and upper tracheobronchial regions, whereas smaller particles (e.g., $PM_{2.5}$) show greater deposition in the deep lung and have a high surface area-to-mass ratio, potentially leading to enhanced biological toxicity.[35]

To our knowledge, all previous published studies have used maternal residence to assess ambient air pollutant exposure. Exposure misclassification could have arisen because we only estimated outdoor exposure at the residential address, without considering the time spent in different microenvironments.[36,37] In a recent study in Barcelona, 54 pregnant women carried a personal $PM_{2.5}$ sampler for 2 days and reported they spent 60–70% time per day at home. The correlation between their outdoor exposure and personal exposure was 0.39 for $PM_{2.5}$.[29,38] This suggests that outdoor levels may not be as good of a surrogate for personal exposure levels, but further evaluation of this question is needed given the small size of the previous study.

Some studies have relied on measurement of exposure at the birth residence rather than the residence early in pregnancy.[7,27,29] Residual misclassification may lead to exposure misclassification if women changed their residences during pregnancy. Some previous studies have shown the residential mobility was 1–6% in four Spanish birth cohort studies,[29,38] 9% in north of England study,[13] 20% in a study in California,[18] and 2.6% in our study. In order to reduce the measurement error, our assessment of maternal exposure to PM was based on maternal residence during the early pregnancy. In addition, our study benefited from using a large sample of women and infants from a perinatal health-care system for Women and Children of Wuhan, and had the advantage of follow-up women from early pregnancy to delivery, thus reducing uncertainties because selection bias and random error misclassification more common in studies with a small sample size.

One limitation of this approach was that the prevalence of CHDs may be underestimated because early fetal loss with CHDs may not been recorded in the system, or because minor defects may be asymptomatic and undetected among neonates, which could have reduced the number of CHD cases. In addition, we did not have data on some other variables that could potentially be confounders, such as maternal diabetes and exposure to passive smoking.

CONCLUSION

Our results showed an increased risk of CHDs in relation to maternal exposure to $PM_{2.5}$, but showed no association between PM_{10} exposure and CHDs, despite the very high levels of PM_{10} among subjects in our study compared to those in previously published studies. This study contributes to the small body of knowledge regarding the association between *in utero* exposure to air pollution and CHDs, but confirmation of these associations will be needed in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We are extremely grateful to all the hospitals and community health centers involved in this study. The study was partly supported by the "Hubei Province Natural Science Foundation Project: Association between air pollution and pregnancy outcome", and the grant number is 2010CDB08803, and partly supported by Fogarty training grants D43TW 008323 and D43TW 007864-01 from the US National Institutes of Health.

REFERENCES

1 World Health Organization. Congenital anomalies. Available on: http://www.who.int/mediacentre/factsheets/fs370/en/ (accessed on January 2014).
2 World Health Statistics, 2013. WHO: Geneva.
3 Chen EK-C, Zmirou-Navier D, Padilla C, Deguen S. Effects of air pollution on the risk of congenital anomalies: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2014; **11**: 7642–7668.
4 Centers for Disease Control and Prevention (CDC). Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. *MMWR Morb Mortal Wkly Rep* 2008; **57**: 1.
5 Yu M, Ping Z, Zhang S, He Y, Dong R, Guo X. The survey of birth defects rate based on birth registration system. *Chin Med J (Engl)* 2015; **128**: 7.
6 Chinese Ministry of Health. Report of birth defects prevention in China; 2012.
7 Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C. Air pollution and congenital heart defects. *Environ Res* 2013; **124**: 28–34.
8 Wu J, Wilhelm M, Chung J, Ritz B. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. *Environ Res* 2011; **111**: 685–692.
9 Lin M-C, Yu H-S, Tsai S-S, Cheng B-H, Hsu T-Y, Wu T-N *et al.* Adverse pregnancy outcome in a petrochemical polluted area in Taiwan. *J Toxicol Environ Health A* 2001; **63**: 565–574.
10 Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. A cohort study of traffic-related air pollution impacts on birth outcomes. *Environ Health Perspect* 2008; **116**: 680.
11 Ha S, Hu H, Roussos-Ross D, Haidong K, Roth J, Xu X. The effects of air pollution on adverse birth outcomes. *Environ Res* 2014; **134**: 198–204.
12 Rankin J, Nieuwenhuijsen M. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. *Environ Health Perspect* 2011; **119**: 599.
13 Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. Association between maternal exposure to ambient air pollution and congenital heart disease: a register-based spatiotemporal analysis. *Am J Epidemiol* 2010; **173**: 171–182.
14 Dolk H, Armstrong B, Lachowycz K, Vrijheid M, Rankin J, Abramsky L *et al.* Ambient air pollution and risk of congenital anomalies in England, 1991-99. *Occup Environ Med* 2009; **67**: 223–227.
15 Ritz B, Wilhelm M. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. *Basic Clin Pharmacol Toxicol* 2008; **102**: 182–190.
16 Ritz B. Air pollution and congenital anomalies. *Occup Environ Med* 2010; **67**: 221–222.
17 Kannan S, Misra DP, Dvonch JT, Krishnakumar A. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential. *Cien Saude Colet* 2007; **12**: 1591–1602.
18 Padula AM, Tager IB, Carmichael SL, Hammond SK, Lurmann F, Shaw GM. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. *Am J Epidemiol* 2013; **177**: 1074–1085.
19 Gilboa S, Mendola P, Olshan A, Langlois P, Savitz D, Loomis D *et al.* Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000. *Am J Epidemiol* 2005; **162**: 238–252.
20 Strickland MJ, Klein M, Correa A, Reller MD, Mahle WT, Riehle-Colarusso TJ *et al.* Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986–2003. *Am J Epidemiol* 2009; **169**: 1004–1014.
21 State Environmental Protection Administration of China (SEPA). Monitoring rules on environmental air quality in China. Available on: http://www.zhb.gov.cn/info/gw/gg/200701/t20070125_100262.htm (accessed on January 2014).
22 Eriksson F. The law of sines for tetrahedra and n-simplices. *Geometriae Dedicata* 1978; **7**: 71–80.
23 Stingone J, Luben T, Daniels J, Fuentes M, Richardson D, Aylsworth A *et al.* Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the National Birth Defects Prevention Study. *Environ Health Perspect* 2014; **122**: 863–872.
24 van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ *et al.* Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011; **58**: 2241–2247.
25 Gittenberger-de Groot AC, Bartelings MM, Deruiter MC, Poelmann RE. Basics of cardiac development for the understanding of congenital heart malformations. *Pediatr Res* 2005; **57**: 169–176.
26 Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P *et al.* Traffic-related air pollution and congenital anomalies in Barcelona. *Environ Health Perspect* 2014; **122**: 317.
27 Vinikoor-Imler LC, Davis JA, Meyer RE, Luben TJ. Early prenatal exposure to air pollution and its associations with birth defects in a state-wide birth cohort from North Carolina. *Birth Defects Res A Clin Mol Teratol*2013; **97**: 696–701.
28 Hansen CA, Barnett AG, Jalaludin BB, Morgan GG. Ambient air pollution and birth defects in Brisbane, Australia. *PloS One* 2009; **4**: e5408.
29 Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. Ambient air pollution and congenital heart disease: a register-based study. *Environ Res* 2011; **111**: 435–441.
30 Shah PS, Balkhair T. Air pollution and birth outcomes: a systematic review. *Environ Int* 2011; **37**: 498–516.
31 Dolk H, Vrijheid M. The impact of environmental pollution on congenital anomalies. *Br Med Bull* 2003; **68**: 25–45.
32 Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. Ambient air pollution and risk of birth defects in Southern California. *Am J Epidemiol* 2002; **155**: 17–25.
33 Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA *et al.* Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environ Health Perspect* 2013; **121**: 267–373.
34 Polichetti G, Capone D, Grigoropoulos K, Tarantino G, Nunziata A, Gentile A. Effects of ambient air pollution on birth outcomes: an overview. *Crit Rev Environ Sci Technol* 2013; **43**: 1223–1245.
35 Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M *et al.* Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 2004; **109**: 2655–2671.
36 Briggs D. The role of GIS: coping with space (and time) in air pollution exposure assessment. *J Toxicol Environ Health A* 2005; **68**: 1243–1261.
37 Jerrett M, Finkelstein M. Geographies of risk in studies linking chronic air pollution exposure to health outcomes. *J Toxicol Environ Health A* 2005; **68**: 1207–1242.
38 Estarlich M, Ballester F, Aguilera I, Fernández-Somoano A, Lertxundi A, Llop S *et al.* Residential exposure to outdoor air pollution during pregnancy and anthropometric measures at birth in a multicenter cohort in Spain. *Environ Health Perspect* 2011; **119**: 1333–1338.

Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (http://www.nature.com/jes)