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Abstract

Background: Maternal exposure to ambient air pollution has been associated with increased risk of congenital heart defects in offspring, however the results are inconsistent.

Objectives: We estimated whether there is an association between prenatal exposure to PM_{10} during early pregnancy and fetal cardiovascular malformations.

Methods: The gravidae from a hospital-based case-control study in Fuzhou, China during 2007–2013 were assigned 10-day or 1-month averages of daily particulate matter with diameter ≤ 10 µm (PM_{10}) using an air monitor-based inverse distance weighting method during early pregnancy. A total of 662 live-birth or selectively terminated cases and 3,972 live-birth controls were enrolled. The exposure was considered as a categorical variable. A multivariable logistic regression model was constructed to quantify the adjusted odds ratios of the exposure to PM_{10} and the risks of fetal cardiovascular malformations.

Results: PM_{10} levels were positively associated with the risks of atrial septal defect (adjusted odds ratios (aOR) ranging from 1.29 to 2.17), patent ductus arteriosus [aORs = 1.54, 1.63; 95% confidence intervals (CIs): (1.17, 2.23), (1.06, 3.24)], overall fetal cardiovascular malformations (aOR = 1.28; 95% CI: 1.03, 1.61), ventricular septal defect (aOR = 1.19; 95% CI: 1.00, 1.43) and tetralogy of Fallot (aOR = 1.44; 95% CI: 1.01, 2.19) in the various observed periods scaled by 10 days or 1 month in the first and second gestation months. The strongest associations were observed for exposure to PM_{10} in the second quartile, while the associations were attenuated when higher concentrations of PM_{10} in the third and fourth quartiles of the exposure were evaluated. No correlations of PM_{10} levels with these cardiovascular malformations in the other time periods of gestation were observed.

Conclusions: Our findings suggest some positive associations between maternal exposure to ambient PM_{10} during the first two months of pregnancy and fetal cardiovascular malformations.

Introduction

A growing body of epidemiological literature has suggested an association between ambient particulate matter (PM) exposure and fetal anomalies, particularly cardiovascular malformations. Evidence has indicated associations between in utero exposure to PM with an aerodynamic diameter less than 10 micrometers (PM_{10}) and the prevalence of fetal cardiovascular malformations, i.e., PM_{10} and ventricular septal defects, pulmonary valve stenosis (Padula et al. 2013), patent ductus arteriosus (Strickland et al. 2009) and multiple congenital heart defects (Agay-Shay et al. 2013). A meta-analysis of air pollutant-anomaly combinations found that PM_{10} exposure was related to an increased risk of atrial septal defects (Vrijheid et al. 2011). Evidence from a line of studies, however, failed to demonstrate an association between PM_{10} and fetal cardiovascular malformations (Ritz et al. 2002; Schembari et al. 2014; Stingone et al. 2014), and no definite link was indicated between ambient total suspended particles and congenital heart diseases in Brindisi, Italy (Gianicolo et al. 2014). An inverse association was reported between PM_{10} and ventricular septal defects (Hansen et al. 2009), and between fine particulate matter ($PM_{2.5}$, with an aerodynamic diameter less than 2.5 micrometers) and atrial septal defects (Stingone et al. 2014), ventricular septal defects (Padula et al. 2013), or isolated patent ductus arteriosus (Agay-Shay et al. 2013). These inconsistent results may be attributed to heterogeneity in the sources, components and exposure levels of PM, methods applied, and differences in demography, topography, meteorology, socioeconomic status and individual lifestyle of the population surveyed (Gorini et al. 2014).

China has been experiencing exceptionally high levels of air pollution in recent years. A few metropolitan areas are among the most polluted in the world, with daily levels of PM_{10} averaged at 144.6 μg/m^3 during 2004-2008 in Beijing (Guo et al. 2013) and 216-293 μg/m^3 in autumn in Shanghai (Zhou et al. 2012). Annual levels of PM_{10} have exceeded 100 μg/m^3 in about one-third of the cities which have been covered by the China National Ambient Air Quality Surveillance Network (Yang et al. 2011). PM_{10} is the only inhalable particulate matter that had been continuously monitored before the year of 2012 within major cities in China. In Fuzhou, the capital city of Fujian Province, ambient PM_{10} levels vary with daily levels about 60-80 μg/m^3. This may represent average levels across the majority of the cities in mainland China (Yang et al. 2011).

Rates of birth defects in China have been reported at 5.12%, which is higher than that in developed countries (Christianson et al. 2006). Birth defect rates have been higher in the coastal/eastern regions and in urban areas where environmental pollution, especially ambient air pollution, is more severe than in western regions and in rural areas (Ministry of Health, People's Republic of China 2011). Cardiovascular malformations, the most frequent types of anomalies in fetuses and neonates, are the main causes of infant mortality (Dadvand et al. 2011b). In China, a national survey reported a prevalence of 7 to 8 cases of congenital heart diseases per 1,000 live births (China National Center for Cardiovascular Disease 2006). There have been few studies, however, regarding particulate air pollution on cardiovascular malformations in China. The air quality in China has been deteriorating over the last several decades due to booming of the economy, with a significant impact globally, particularly on the neighboring countries. In the present study, we investigated whether there was an association between exposure to PM_{10} and risks of fetal cardiac malformations by a hospital-based retrospective case-control design.

Methods

Study area

Fuzhou is the capital city of Fujian Province, and is located in the coastal area of southeastern China. The city is surrounded northeast, northwest and southwest by hills and mountains and faces southeast to the Taiwan Strait, with an administrative area of 11,968 square kilometers and a population of 6.24 million. The built-up region of Fuzhou, which is the central area in the city with an area about 200 square kilometers, consists of a population of 1.95 million according to the Sixth National Population Census Fuzhou in 2010 (Figure 1). A built-up region is generally the central area of urban field with the densest population. The built-up region of Fuzhou is relatively small compared to the entire city area (Figure 1). Fuzhou has a wet, monsoon-influenced humid marine climate, characterized by a long summer and winter and short spring and autumn. The temperature averages 19.6°C, with precipitation of 1,348.8 mm between 2007 and 2013. Ambient air pollution, including airborne PM, is among the average levels in China.

Study population

We collected the data from pregnant women who resided in Fuzhou, China during their pregnancy and were gestationally monitored and delivered at Fujian Maternity and Children Health Hospital or Fuzhou General Hospital. Both hospitals are big Grade A tertiary hospitals in Fuzhou, Fujian Province with a total of about 15,000 births annually, which accounts for nearly 2/3 of the total annual births in the built-up region of Fuzhou. All of the data came from prenatal care and parturition records of the pregnant women of who delivered or selected termination at ≥ 20 gestation weeks, with an estimated date of conception between January 1, 2007 and December 31, 2013. A total of 110,720 births were enrolled for the selection of cases and controls, in which 99,094 births (89.5%) lived in the built-up region of Fuzhou. The date of conception was estimated based on the hospital records (date of birth and gestational age) by assuming that the conception occurred 14 days after the last menstrual period date. The Scientific Research Committees and Ethics Committees of Fuzhou General Hospital and Fujian Maternity and Children Health Hospital approved the study involving the use of the hospital records.

Cases consisted of a cohort clinically diagnosed with birth defects. We recorded the details regarding premature delivery, stillbirth and term birth, ≥ 20 weeks late abortion and ≥ 20 weeks with antenatal diagnosis of congenital malformations. We also documented the mother's general conditions, including age, gravidity, parity, last menstrual period, residential address, history of abnormal pregnancy and labor, trimester in which prenatal care began, medication, concomitant disease(s), and if any, living habit, psychological status, nutritional status, and diets. The data of infants with any indications of fetal anomalies were also obtained from the hospital records. Fetal malformations were confirmed by echocardiogram, cardiac catheter surgical operation and/or autopsy, with reference to ultrasonic examination, cytogenetic examination, medication administration records and follow-up materials, whenever available.

Cases were excluded when they met one of the following criteria (Bassili et al. 2000; Jenkins et al. 2007; Strickland et al. 2009): (1) missing important records of medical history, including equivocation of conceptus age (9 cases that met the criteria), (2) maternal ill-conditions, including gestation weeks <20 or >44, gestational diabetes or diabetes with pregnancy, congenital cardiopathy with pregnancy, conditions of illness with fever (>38ºC) or exposure to pesticides within 3-8 gestation weeks, or history of consanguineous mating or genetic defects (18 cases), (3) twin pregnancy (6 cases), and (4) isolated patent ductus arteriosus in premature birth (5 cases).

Controls were randomly selected from the total live-born and non-malformed infants by the date of birth sampling, which were independent of the cases at a ratio of 1:6 (case:control) to meet an accepted statistical power. Data for the control samples were derived from the medical records of the gravidae and the birth records from the two hospitals enrolled. All of the newborns in the control group were routinely examined to rule out cardiovascular malformations and other major anomalies.

Data for the numbers of fetal defects, ages of the pregnant women, parity and longitude and latitude of gravida's habitation, the pregnant women grouping based on their ages, season of conception and diagnoses for fetal malformations were collected and entered manually into an EpiData 3.0 database created by EpiData software (EpiData Association, Odense, Denmark). These data came from the hospital records and birth records.

Classification of fetal cardiovascular malformations

Cardiovascular malformations were diagnostically categorized as nine subtypes, i.e., ventricular septal defect, atrial septal defect, patent ductus arteriosus, coarctation of aorta, pulmonary valve stenosis, tetralogy of Fallot, hypoplastic left heart syndrome, transposition of conducting arteries and other seldom subtypes such as ectopia cordis, ventricular double outlets, tricuspid atresia, inborn aortic arch anomalies, etc. (Strickland et al. 2009). The concomitance of cardiovascular abnormalities was recognized and counted only if these abnormalities were embryologically independent from each other (Riehle-Colarusso et al. 2007; Strickland et al. 2009). Temporarily isolated cardiovascular conditions in neonates, such as patent oval foramen, were considered as normal, and the neonates with identified trisomies, heterotaxy syndrome or abnormal cardiac looping were not counted (Riehle-Colarusso et al. 2007; Strickland et al. 2009). Cardiovascular abnormalities in combination with simultaneous fetal anomalies other than the cardiovascular system were excluded from further analyses because they might have more complicated causes (Agay-Shay et al. 2013).

Ambient PM_{10} levels and estimation of maternal exposure to PM_{10}

Ambient PM_{10} levels were quantified by the Central Station of Environmental Monitoring of Fujian Province. PM_{10} levels were monitored and recorded hourly from three monitoring stations within the built-up region of Fuzhou, namely Wusibei, Ziyang and Shida, all of which are parts of the China National Ambient Air Quality Surveillance Network (Figure 1). Daily, monthly and seasonal average levels of PM_{10} between January 1, 2007 and December 31, 2013 were calculated based on these measurements.

The residential address of each gravida during pregnancy was converted into longitude and latitude using Google map software (version 7.6.1) according to a detailed address, including house number, street and block (Dadvand et al. 2011a). To estimate the individual PM_{10} exposure level, a station-based inverse distance weighting interpolation method was applied to interpolate the daily PM_{10} concentrations from the three monitoring stations to the predicted residential site across Fuzhou (Padula et al. 2013). For each monitoring site, $\lambda = 1/d^2$ was used as the weighting factor, where “d” refers to the distance between the monitoring site and the predicted residential site (Wong et al. 2004). Data from the three monitoring stations were included in each interpolation. While transferring the data from the cases and controls and the corresponding PM_{10} levels into the database, logistic rectification, which was tested automatically and was manually rectified as soon as an error was found, was used to identify and correct potential errors in the data entry.

Statistical analysis

The 24-hour measurements of PM_{10}, hospital-based birth certificates and birth defect records were used for analyses. Maternal exposure and risk factors were classified at the individual level. The risk of fetal cardiovascular malformations versus PM_{10} exposure was analyzed by incorporating the variables using multivariable logistic regression analyses. Maternal education was coded as one of the three categories: ≤ primary school, junior or senior high school and ≥ college education. Seasons of conception were categorized as warm (May–October) or cool (November–April) based on the local climate condition. The trimester in which prenatal care began was categorized as the first, second, third trimester or no care. Maternal variables, such as psychological status, nutritional status, prenatal folic acid and vitamin use, marital status, and history of abnormal pregnancy and labor, were treated as the dichotomous variables (Rankin et al. 2009). Potential covariates from the hospital records, which included maternal age, parity, educational attainment, prenatal care, prenatal folic acid and vitamin use, season of conception and marital status, were entered for the final adjustments based on the previous studies (Agay-Shay et al. 2013; Myers et al. 2011; Padula et al. 2013) and the data available in Fuzhou, China.

Potential deviations in the estimation of the conception date may produce greater bias by using a shorter time scale for the analyses. Time lag may exist between the exposure and its response to the body. Considering these factors, we analyzed associations by a ten-day scale, instead of 7 days (one week), over postconception days 11-60 to increase the stability of the results. The association was analyzed by categorizing the exposure duration as 11-20, 21-30, 31-40, 41-50, 51-60 gestation days, and the first and second months of the gestation. PM_{10} exposure estimates were examined as quartiles using the distribution among the controls. Since PM_{10} exposure estimates were verified to be normally distributed, they were entered into the regression model as categorical variables on the basis of the quartile distribution. The first quartile was used as a reference, and the other higher quartiles were compared with the reference to calculate the adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs).

Comparisons were conducted in the subgroups of ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, and overall cardiovascular malformations because they consisted of relatively large sample sizes. Data were analyzed using SPSS17.0 software and statistical package STATA (versions 10.1, StataCorp, College Station, TX, USA).

Results

Descriptive statistics

Daily PM_{10} levels in Fuzhou ranged between 7 and 1,034 $\mu g/m^3$, with one day peaking at 1,034 $\mu g/m^3$, four days above 250 $\mu g/m^3$ and 54 days (7.7 days per year) above 150 $\mu g/m^3$, the criteria of the US Environmental Protection Agency, between January 1, 2007 and December 31, 2013. The monthly levels were usually higher from February to April within a year, with the highest at 137 $\mu g/m^3$ in February 2010. The seasonal levels of PM_{10} ranged between 40 and 99.8 (mostly

44 – 80) μg/m^3, with the highest in the spring or summer and lowest in the autumn, which are delineated in Figure 2.

All of the enrolled participants were Han, the ethnic majority in China. Before the exclusions, there was a liveborn and stillborn cohort of 110,720 births in Fujian Maternity and Children Health Hospital and Fuzhou General Hospital, with the estimated date of conception during January 1, 2007 and December 31, 2013. Among the 110,720 births, fetal malformations were diagnosed in 1,584 births without the evidence of trisomy. The overall prevalence of fetal malformations was 1.43% with an increasing tendency from 2007 to 2013 (see Table S1).

There were 700 cases that were subjected to fetal cardiovascular malformations in the 1,584 cases with fetal malformations (see Table S2). The subtypes of fetal cardiovascular malformations were ranked in a frequency order from high to low as ventricular septal defect, atrial septal defect, patent ductus arteriosus, tetralogy of Fallot and others (Table 1).

Correlations of PM_{10} exposure levels and risks for fetal cardiovascular malformations

Following screening according to the exclusion criteria, 38 cases that met the exclusion criteria were excluded from entering the final analyses. There were 662 out of the 700 cases with fetal cardiovascular malformations entering the final analyses, in which 638 cases (96.4%) lived in the built-up region of Fuzhou. The remaining 24 cases, including one 41 km, one 33 km and the others within 15-25 km far from the nearest monitoring station, lived outside the built-up region. Locations of the pregnant women were geographically stochastically distributed in the City of Fuzhou other than proximal to the two hospitals. The local main emission sources are the traffic and living sources, which are distributed roughly evenly throughout the observed region, and there are no major emission sources coming from heavy industrial sectors in the region and nearby. Therefore, there was no tendency of the mothers with different socioeconomic status to selectively distribute in the places with different levels of PM_{10}. The general conditions of the cases and controls, including the age, parity and distribution of their residential sites, are presented in Table S3.

As shown in Table 2, PM_{10} exposure levels were associated with the risks of atrial septal defect (aOR = 2.07, 95% CI: 1.19, 3.22), and patent ductus arteriosus (aOR = 1.59, 95% CI: 1.03, 3.00) in the second gestation month. Divided by shorter time scales (ten days), we observed elevated risks for atrial septal defect with aORs ranging between 1.29 and 2.17, patent ductus arteriosus with aORs at 1.54 (95% CI: 1.17, 2.23) and 1.63 (95% CI: 1.06, 3.24) in the various observed periods, overall fetal cardiovascular malformations (aOR = 1.28; 95% CI: 1.03, 1.61) in gestation day 41-50, ventricular septal defect (aOR = 1.19; 95% CI: 1.00, 1.43) in gestation day 41-50, and tetralogy of Fallot (aOR = 1.44; 95% CI: 1.01, 2.19) in gestation day 31-40. We also observed an increased risk for atrial septal defect (aOR = 1.29; 95% CI: 1.05, 1.74) at gestation day 21-30, despite the absence of the increased risk in the first gestation month. Interestingly, the effect estimates were generally observed to be the highest in the second quartile with the exposure levels ranging from 41.9 to 75.5 $\mu g/m^3$ and then attenuated in the third and fourth quartiles at higher exposure levels.

Discussion

In the present study, we estimated associations between maternal exposure to ambient PM_{10} during the first two months of pregnancy from 2007 to 2013 and the risks of fetal cardiovascular malformations. Our results indicate that exposure to ambient PM_{10} during early gestation may be associated with increased risks of fetal cardiovascular malformations in the observed time period in Fuzhou, China. The associations between maternal gestational exposure to PM_{10} and atrial septal defect, fetal patent ductus arteriosus and overall congenital heart malformations, provide further evidence that prenatal exposure to air pollution is associated with risks for fetal heart malformations.

The aORs in the second quartiles were higher than those in the third and fourth quartiles for the trends in most of the results as indicated in Table 2. This may suggest a nonmonotonic exposure response relating to other competing birth outcomes, such as spontaneous abortions and stillbirths, which are not considered in the present study (Gianicolo et al. 2014; Padula et al. 2013; Ritz et al. 2002; Vrijheid et al. 2011). As 3 – 8 gestation weeks are the critical window for the formation of fetal cardiac chambers and inflow and outflow tracks, we intended to collect all the cases that were exposed to PM_{10} during this time period. However, early PM_{10} exposure during gestation may increase the risk of fetal abortion less than 20 weeks of gestation (Strickland et al. 2009). We therefore might miss important data from these cases in our analyses. This may be one of the causes resulting in higher aORs in the second quartiles compared to those in the third or fourth quartiles in our results. Paradoxical reversal of the risks for fetal cardiovascular malformations by excessively high levels of PM_{10} (Zhang et al. 2016) might also possibly be interpreted as a result of nonmonotonic exposure response, which seems to be coincident with the nonlinearity of our results.

There are a number of studies that have investigated maternal exposure to ambient PM_{10}, with combination of other air pollutants, and fetal congenital heart defects. Some original studies have reported increased risks of atrial septal defects (Gilboa et al. 2005; Hwang et al. 2015), patent ductus arteriosus (Strickland et al. 2009) and tetralogy of Fallot (Dolk et al. 2010) associated with maternal PM_{10} exposure. Our results were consistent with the results from these reports. In addition, our results also suggested a possible adverse association between PM_{10} exposure and ventricular septal defect, which also coincides with a previous report (Padula et al. 2013). The correlations between PM_{10} exposure and the risk of fetal heart malformations seemed to be comparable or stronger, and the exposure levels of PM_{10} were higher than what was reported by Gilboa et al. (aOR = 2.27; 95% CI: 1.43, 3.60 for isolated atrial septal defects; first quartile < 19.5 μg/m^3 and fourth quartile ≥ 29 μg/m^3), Strickland et al. (OR = 1.60, 95% CI: 1.11, 2.31 for patent ductus arteriosus; daily PM_{10} levels between 25.8-43.2 μg/m^3), Padula et al. ($aOR_{3rd\ Quartile}$ = 2.1, 95% CI: 1.1, 3.9 for perimembranous ventricular septal defects; daily PM_{10} exposure levels 7.9-25.2 μg/m^3), and Hwang et al. ($OR_{4rd\ Quartile}$ = 2.52, 95% CI: 1.44, 4.42 for atrial septal defects; averaged PM_{10} level 56.6 μg/m^3). One report indicated an increased risk for tetralogy of Fallot in relation to PM_{10} exposure (OR = 1.48, 95% CI: 0.57, 3.84) (Dolk et al. 2010). Our results showed a similar aOR value at 1.44 for PM_{10} exposure versus tetralogy of Fallot. A meta-analysis supported the correlation between maternal PM_{10} exposure and the increased risk of atrial septal defects (OR = 1.14, 95% CI: 1.01, 1.28 for each 10 μg/m^3 increase) (Vrijheid et al. 2011). However, this was not confirmed by another meta-analysis conducted more recently (Chen et al. 2014).

Several reports with regard to PM_{10} exposure and congenital heart defects did not observe a positive association (Dadvand et al. 2011a; Hansen et al. 2009; Ritz et al. 2002; Schembari et al. 2014; Stingone et al. 2014; Vinceti et al. 2016). Most of these reports had low PM_{10} exposure levels, i.e., averaged at 18 μg/m^3 (Hansen et al. 2009), < 14.9 μg/m^3 for < 10th centile and > 40.6

μg/m^3 for ≥ 90th centile (Stingone et al. 2014), a median of 38.7 μg/m^3 (Schembari et al. 2014), and minimum 7.1 μg/m^3 to maximum 50.4 μg/m^3 (Dadvand et al. 2011a) compared to those presented in the current study, except for one recent report by Zhang et al., in which the mean PM_{10} level was 101.7 μg/m^3 (Zhang et al. 2016). Our results suggested that adverse associations between PM_{10} exposure and fetal cardiovascular malformations could also be observed during gestation days 21-30 (atrial septal defect), the earlier stage in which formation of the fetal heart occurs. Agay-Shay reported an association between maternal PM_{10} exposure and multiple congenital heart defects, but not isolated atrial and atrial septal defects, ventricular septal defect or patent ductus arteriosus, at an average PM_{10} exposure level of 58.8 μg/m^3 (Agay-Shay et al. 2013). One study did not report the PM_{10} exposure level (Ritz et al. 2002). Although there were various factors affecting the results, we considered a higher level of PM_{10} exposure, which was 2.4-4.1 times higher than the exposure levels reported by most other studies during early pregnancy, thus would exert greater toxicities associated with fetal heart malformations. However, exorbitantly high level exposure to PM_{10} might have reverse correlations with fetal cardiovascular malformations (Zhang et al. 2016), which is likely to be attributable to a nonlinear correlation between PM_{10} exposure and its cardiovascular effects.

Ventricular septal defect is the most common subtype of cardiovascular malformations, with a prevalence similar to the report by Strickland et al. (Strickland et al. 2009). The proportions for ventricular septal defect and atrial septal defect were comparable to, whereas the proportions for patent ductus arteriosus and tetralogy of Fallot were higher than those in the reports (Agay-Shay et al. 2013; Dadvand et al. 2005; Gilboa et al. 2005; Schembari et al. 2014; Strickland et al. 2009). The differences existing between our study and other similar studies may come from the differences in the sample collection and disease definition used. We have used term infants with patent ductus arteriosus persisting for ≥4 weeks after birth, compared to ≥6 weeks in the study by Strickland (Strickland et al. 2009). Furthermore, our hospital-based sampling was derived from a relatively small region with limited representatives for the population of congenital heart defects, which might be another cause of the discrepancy in proportions.

We have included about two-third of the regional births in our study. The remaining one-third of births with their mothers who entered other hospitals were not significantly different from the ones in our hospitals in the mothers' socioeconomic statuses, and the different residencies of the mothers enrolled did not correlate with their socioeconomic statuses. A few pregnant women might transfer to a grade A hospital from a lower grade hospital when a complicated pregnancy condition is found. Considering small percentage of the gravidae in the lower grade hospitals and small percentage of the gravidae who were subjected to abnormal pregnancy including fetal cardiovascular malformations, the discrepancies among the gravidae choosing different grade hospitals, if existed, would not significantly alter the outcomes in our analyses.

There are several limitations in the present study. Although we used a geographic technique coupled with inverse distance weighting method to evaluate the exposure levels, this model and the analyses based on the exposure estimates from the ambient monitoring network has been reported to produce somewhat wider 95% CIs compared to the effect estimates based on land use regression models with yet similar estimates of the effect among them (Brauer et al. 2008). The present case-control study was based on the cases with pregnant duration ≥ 20 weeks. Some gravidae were excluded from the analyses, which might incur bias in our results. No maternal residential history during the pregnancy was available. We took only residential information from their medical records at early stages of pregnancy regardless of possible residential changes during the pregnancy. This might result in some deviation of the exposure assessment with bias in an unknown direction, although reports showed no obvious impact on the assessment resulting from the change of the living addresses during pregnancy (Lupo et al. 2010). Additional unmeasured covariates, such as socioeconomic status, living habit and dietary factors of the gravidae, could have affected our results, whereas we did not evaluate the co-effects from these factors in our analyses due to the limitation of relevant data. The temporal factors in our study design with the data from a limited number of monitoring stations might also compromise our exposure evaluation. We did not investigate other subtypes of cardiovascular malformations except for the four major subtypes owing to the inadequate sample sizes and might thus miss their possible associations with PM_{10} exposure. PM_{10} was found to be associated with pulmonary valve stenosis (Padula et al. 2013). Agay-Shay reported an association of maternal exposure to increased concentrations of PM_{10} with multiple congenital heart defects (Agay-Shay et al. 2013). The associations were found between in utero exposure to $PM_{2.5}$, but not coarse particulate matter with an aerodynamic diameter of 10-2.5 micrometers, and hypoplastic left heart syndrome (Stingone et al. 2014) or transposition of the great arteries (Padula et al. 2013). We did not observe these associations due to the relatively small sample sizes.

A gravida generally lives inside the house during gestation, and indoor PM_{10} levels might be very different from outdoor PM_{10} levels, especially in developing countries (Ezzati and Kammen 2002). This potentially overestimates, or more possibly, underestimates the exposure that could bias our effect estimates. We assigned the exposure using merely the geographic technique regardless of the impact from local meteorological factors, traffic factors, social geography, and spatio-temporal activity patterns of individual gravida. More importantly, we did not investigate the co-effects from other air pollutants such as carbon monoxide, nitrogen dioxide and ozone, which are associated with fetal heart development (Gilboa et al. 2005). Therefore, our data did not represent all of the major air pollutants emitted and transported, which is another limitation in our study. $PM_{2.5}$ levels were routinely monitored beginning from year 2012 in Fuzhou, China. As we lacked the entire serial monitoring data of $PM_{2.5}$ during the study period, we could not evaluate the health impact of $PM_{2.5}$ exposure in the present work.

Conclusions

In conclusion, exposure to ambient levels of PM_{10} during early pregnancy was indicated to be associated with fetal cardiovascular malformations. The most significant association was found in the second quartile of the exposure levels between 41.9 and 75.5 $\mu g/m^3$ and then attenuated in the third and fourth quartiles at the higher exposure levels. Our findings are important and have potential impact on public health and policy-making for emerging countries including China, whose standard criteria were revised in 2012 as daily PM_{10} levels at 50, 150 $\mu g/m^3$ and annual PM_{10} levels at 40, 70 $\mu g/m^3$ (Grade I, II), respectively (Ministry of Environmental Protection, People's Republic of China 2012) and stricter criteria may be needed in the near future.

References

Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C. 2013. Air pollution and congenital heart defects. Environ Res 124:28–34.

Bassili A, Mokhtar SA, Dabous NI, Zaher SR, Mokhtar MM, Zaki A. 2000. Risk factors for congenital heart diseases in Alexandria, Egypt. Eur J Epidemiol 16:805-814.

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect 116:680–686.

Chen EK, Zmirou-Navier D, Padilla C, Deguen S. 2014. Effects of air pollution on the risk of congenital anomalies: A systematic review and meta-analysis. Int J Environ Res Public Health 11:7642-7668.

China National Center for Cardiovascular Disease. 2006. Chinese cardiovascular disease report 2005. Beijing: Encyclopedia of China Publishing House. 103-105.

Christianson A, Howson CP, Modell B. 2006. March of Dimes Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children. Available: http://www.marchofdimes.com/downloads/Birth_Defects_Report-PF.pdf [accessed 15 February 2012].

Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. 2011a. Ambient air pollution and congenital heart disease: A register-based study. Environ Res 111:435-441.

Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. 2011b. Association between maternal exposure to ambient air pollution and congenital heart disease: A register-based spatiotemporal analysis. Am J Epidemiol 173:171–182.

Dai L, Zhu J, Liang J, Wang YP, Wang H, Mao M. 2011. Birth defects surveillance in China. World J Pediatr 7:302-310.

Dolk H, Armstrong B, Lachowycz K, Vrijheid M, Rankin J, Abramsky L, et al. 2010. Ambient air pollution and risk of congenital anomalies in England, 1991-1999. Occup Environ Med 67:223-227.

Ezzati M, Kammen DM. 2002. The health impacts of exposure to indoor air pollution from solid fuels in developing countries: knowledge, gaps, and data needs. Environ health perspect 110:1057-1068.

Gianicolo EA, Mangia C, Cervino M, Bruni A, Andreassi MG, Latini G. 2014. Congenital anomalies among live births in a high environmental risk area--a case-control study in Brindisi (southern Italy). Environ Res 128:9-14.

Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D, et al. 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am J Epidemiol 162:238-252.

Gorini F, Chiappa E, Gargani L, Picano E. 2014. Potential effects of environmental chemical contamination in congenital heart disease. Pediatr Cardiol 35:559-568.

Guo Y, Li S, Tian Z, Pan X, Zhang J, Williams G. 2013. The burden of air pollution on years of life lost in Beijing, China, 2004-08: Retrospective regression analysis of daily deaths. BMJ 347:f7139.

Hansen CA, Barnett AG, Jalaludin BB, Morgan GG. 2009. Ambient air pollution and birth defects in Brisbane, Australia. PloS One 4:e5408.

Hwang BF, Lee YL, Jaakkola JJ. 2015. Air pollution and the risk of cardiac defects: A population-based case-control study. Medicine (Baltimore) 94:e1883.

Jacobs ML. 2000. Congenital heart surgery nomenclature and database project: Tetralogy of Fallot. Ann Thorac Surg 69:S77-S82.

Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, 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: Endorsed by the American Academy of Pediatrics. Circulation 115:2995-3014.

Lupo PJ, Symanski E, Chan W, Mitchell LE, Waller DK, Canfield MA, et al. 2010. Differences in exposure assignment between conception and delivery: The impact of maternal mobility. Paediatr Perinat Epidemiol 4:200-208.

Ministry of Environmental Protection, People's Republic of China. GB3095-2012 Ambient Air Quality Standard. 2012. Available: http://wenku.baidu.com/link?url=Rbc0AnsLogD8nxHDnlrzWOeLgjXmc3bqUOuqM3Cd0fIgOJshbD2Ox4AvQ7FlKrFhJVx0ZojtX1nzbczSZCKPyhygw4CCBZrXd9pG6pFn4W7

Ministry of Health, People's Republic of China. 2011. Report on women and children's health development in China. Available: http://www.docin.com/p-454460607.html

Myers JA, Rassen JA, Gagne JJ, Huybrechts KF, Schneeweiss S, Rothman KJ, et al. 2011. Effects of adjusting for instrumental variables on bias and precision of effect estimates. Am J Epidemiol 174:1213–1222.

Padula AM, Tager IB, Carmichael SL, Hammond SK, Yang W, Lurmann F, et al. 2013. Ambient air pollution and traffic exposures and congenital heart defects in the San Joaquin Valley of California. Paediatr Perinat Epidemiol 27:329-339.

Rankin J, Chadwick T, Natarajan M, Howel D, Pearce MS, Pless-Mulloli T. 2009. Maternal exposure to ambient air pollutants and risk of congenital anomalies. Environ Res 109:181-187.

Riehle-Colarusso T, Strickland MJ, Reller MD, Mahle WT, Botto LD, Siffel C, et al. 2007. Improving the quality of surveillance data on congenital heart defects in the Metropolitan Atlanta Congenital Defects Program. Birth Defects Res A Clin Mol Teratol 79:743–753.

Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. 2002. Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol 155:17-25.

Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P, et al. 2014. Traffic-related air pollution and congenital anomalies in Barcelona. Environ Health Perspect 122:317-323.

Stingone JA, Luben TJ, Daniels JL, Fuentes M, Richardson DB, Aylsworth AS, 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 122:863-872.

Strickland MJ, Klein M, Correa A, Reller MD, Mahle WT, Riehle-Colarusso TJ, et al. 2009. Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986-2003. Am J Epidemiol 169:1004-1014.

Vinceti M, Malagoli C, Malavolti M, Cherubini A, Maffeis G, Rodolfi R, et al. 2016. Does maternal exposure to benzene and PM10 during pregnancy increase the risk of congenital anomalies? A population-based case-control study. Sci Total Environ 541:444-450.

Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, et al. 2011. Ambient air pollution and risk of congenital anomalies: A systematic review and meta-analysis. Environ Health Perspect 119:598-606.

Wong DW, Yuan L, Perlin SA. 2004. Comparison of spatial interpolation methods for the estimation of air quality data. J Expo Anal Environ Epidemiol 14:404-415.

Yang F, Tan J, Zhao Q, Du Z, He K, Ma Y, et al. 2011. Characteristics of $PM_{2.5}$ speciation in representative megacities and across China. Atmos Chem Phys 11:5207-5219.

Zhang B, Liang S, Zhao J, Qian Z, Bassig BA, Yang R, et al. 2016. Maternal exposure to air pollutant PM2.5 and PM10 during pregnancy and risk of congenital heart defects. J Expo Sci Environ Epidemiol doi: 10.1038/jes.2016.1. [Epub ahead of print]

Zhou M, Chen C, Wang H, Huang C, Su L, Chen Y, et al. 2012. Chemical characteristics of particulate matters during air pollution episodes in autumn of Shanghai, China. Acta Scientiae Circumstantiae 32:81-92. (Chinese with the English abstract)

Table 1 Subtype and prevalence of fetal cardiovascular malformation groupings from total birth population 110,720 in Fuzhou between 2007 and 2013

Cardiovascular malformations	Number	Prevalence (Subtype/Total birth population, %)	Ratio (Subtype/Total, %)
Ventricular septal defect	270	0.244	38.6
Atrial septal defect	145	0.131	20.7
Patent ductus arteriosus	107	0.097	15.3
Tetralogy of Fallot	81	0.073	11.6
Pulmonary valve stenosis	34	0.031	4.9
Transposition of conducting arteries	26	0.023	3.7
Coarctation of aorta	19	0.017	2.7
Hypoplastic left heart syndrome	14	0.013	2.0
Others	4	0.004	0.6
Total	700	0.632	100.0

Table 2 Adjusted odds ratios (95% confidence intervals) for congenital heart malformations by quartiles for PM_{10} concentrations (μg/m^3) during the first two months of gestation during 2007–2013 in Fuzhou, China (total birth population, 110,720)

Time scale/Quartile of exposure level	Ventricular septal defect (*n* = 261) [a]		Atrial septal defect (*n* = 137)		Patent ductus arteriosus (*n* = 96)		Tetralogy of Fallot (*n* = 75)		Overall fetal cardiovascular malformations (*n* = 662)	
	aORs	95%CI	aORs	95%CI	aORs	95%CI	aORs	95%CI	aORs	95%CI
Days 11-20										
<42.9	1	-	1	-	1	-	1	-	1	-
42.9-<70.5	1.14	0.90, 1.29	1.20	0.78, 1.92	1.18	0.72, 1.51	1.26	0.65, 2.24	1.35	0.78, 2.34
70.5-<118.1	1.09	0.79, 1.63	1.09	0.80, 1.37	1.10	0.89, 1.39	1.07	0.64, 2.09	1.11	0.70, 1.71
≥118.1	0.89	0.66, 1.07	0.98	0.57, 1.61	1.14	0.80, 1.46	1.04	0.65, 1.59	1.15	0.68, 1.78
Days 21-30										
<41.6	1	-	1	-	1	-	1	-	1	-
41.6-<74.7	1.19	0.78, 1.58	1.29	1.05, 1.74	1.27	0.80, 1.60	1.29	0.76, 2.18	1.19	0.67, 1.88
74.7-<120.5	1.14	0.81, 1.53	1.24	0.87, 1.55	1.08	0.74, 1.37	1.13	0.66, 2.17	1.11	0.71, 1.49
≥120.5	0.88	0.67, 1.71	1.12	0.90, 1.52	0.89	0.67, 1.15	1.04	0.77, 1.44	0.99	0.70, 1.47
Days 31-40										
<41.9	1	-	1	-	1	-	1	-	1	-
41.9<73.1	1.21	1.01, 1.53	2.17	1.29, 3.64	1.54	1.17, 2.23	1.44	1.01, 2.19	1.55	0.93, 2.47
73.1-<121.3	1.27	0.88, 1.62	1.33	1.07, 1.85	1.21	0.78, 1.97	1.20	0.76, 1.70	1.29	0.75, 2.08
≥121.3	1.23	0.90, 1.52	1.04	0.79, 1.46	1.07	0.65, 1.82	1.07	0.66, 1.87	1.11	0.70, 1.96
Days 41-50										
<43.1	1	-	1	-	1	-	1	-	1	-
43.1-<75.5	1.19	1.00, 1.43	1.88	1.22, 2.75	1.63	1.06, 3.24	1.22	0.94, 1.59	1.28	1.03, 1.61
75.5-<121.9	1.19	0.87, 1.58	1.18	0.97, 1.63	1.26	0.85, 2.39	1.25	0.83, 1.91	1.12	0.86, 1.41
≥121.9	1.01	0.83, 1.44	1.07	0.88, 1.48	1.11	0.64, 2.06	0.96	0.68, 1.55	1.03	0.84, 1.36
Days 51-60										
<43.1	1	-	1	-	1	-	1	-	1	-
43.1-<74.7	1.11	0.89, 1.38	1.33	0.94, 1.68	1.30	0.79, 1.75	1.39	0.92, 1.86	1.20	0.77, 1.91
74.7-<122.2	0.97	0.79, 1.42	0.92	0.80, 1.35	1.21	0.67, 2.27	1.17	0.67, 1.60	1.23	0.84, 1.76
≥122.2	1.04	0.90, 1.31	1.22	0.95, 1.48	1.05	0.70, 1.71	0.88	0.65, 1.37	1.09	0.73, 1.70

Table 2 *Continued*

Time scale/Quartile of exposure level	Ventricular septal defect (*n* = 261) [a]		Atrial septal defect (*n* = 137)		Patent ductus arteriosus (*n* = 96)		Tetralogy of Fallot (*n* = 75)		Overall fetal cardiovascular malformations (*n* = 662)	
	aORs	95%CI	aORs	95%CI	aORs	95%CI	aORs	95%CI	aORs	95%CI
First month										
<41.1	1	-	1	-	1	-	1	-	1	-
41.1-<73.8	1.16	0.82, 1.50	1.31	0.87, 1.72	1.26	0.95, 1.74	1.33	0.70, 2.06	1.19	0.78, 1.89
73.8-<122.4	1.10	0.79, 1.57	1.08	0.85, 1.31	1.12	0.71, 1.78	1.21	0.59, 2.42	1.16	0.72, 1.78
≥122.4	0.93	0.67, 1.41	1.00	0.61, 1.54	0.90	0.67, 1.31	0.82	0.62, 1.27	1.07	0.68, 1.55
Second month										
<41.9	1	-	1	-	1	-	1	-	1	-
41.9-<74.8	1.17	0.95, 1.47	2.07	1.19, 3.22	1.59	1.03, 3.00	1.32	0.96, 1.78	1.33	0.98, 2.17
74.8-<122.2	1.21	0.84, 1.60	1.44	0.91, 2.05	1.16	0.77, 2.11	1.20	0.79, 1.71	1.31	0.89, 2.20
≥122.2	1.03	0.86, 1.41	1.07	0.87, 1.44	1.10	0.72, 1.89	0.94	0.71, 1.52	1.07	0.78, 1.81

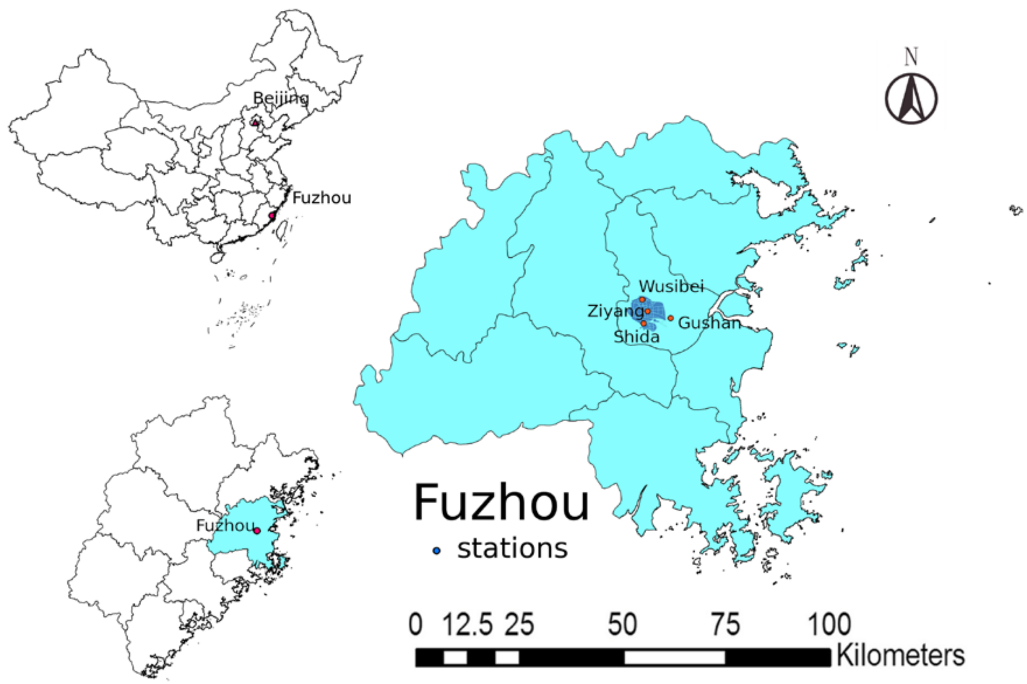
[a] "*n*" refers to the number in the cases. The first quartile was used as a reference and the other higher quartiles were compared with the first quartile, respectively. Models were adjusted for maternal age, parity, educational attainment, prenatal care, prenatal folic acid and vitamin use, season of conception and marital status.

[b] Term infants with patent ductus arteriosus persisting for ≥4 weeks after birth.

Figure captions

Figure 1. Location of monitoring stations in Fuzhou, China. Three monitoring stations are distributed within the built-up region of the city, which is in the central area of Fuzhou with high density of population. One additional monitoring station (Gushan) locates at 450 meters height above the sea level on a mountain outside the built-up region of the city, which serves as the reference for monitoring the background of air pollution. Data obtained from the reference station do not enter the estimating system for evaluation of air quality.

Figure 2. PM_{10} levels in Fuzhou, China during 2007 to 2013. PM_{10} levels in Fuzhou varied dramatically with daily levels averaged at 69.4 μg/m^3. Daily PM10 levels exceeded 250 μg/m^3 on January 9 (263 μg/m^3), February 23 (268 μg/m^3), 2008, March 21 (361 μg/m^3), 23 (522 μg/m^3), 2010, peaked on March 22 (1,034 μg/m^3), 2010, and were as low as 7 μg/m^3 on November 10, 2011 and December 16, 2013. The levels that exceeded 300 μg/m^3 are not fully shown in the figure. The average monthly levels ranged between 56.1 and 72.9 μg/m^3, and the seasonal levels were generally higher in the spring and lower in the autumn.



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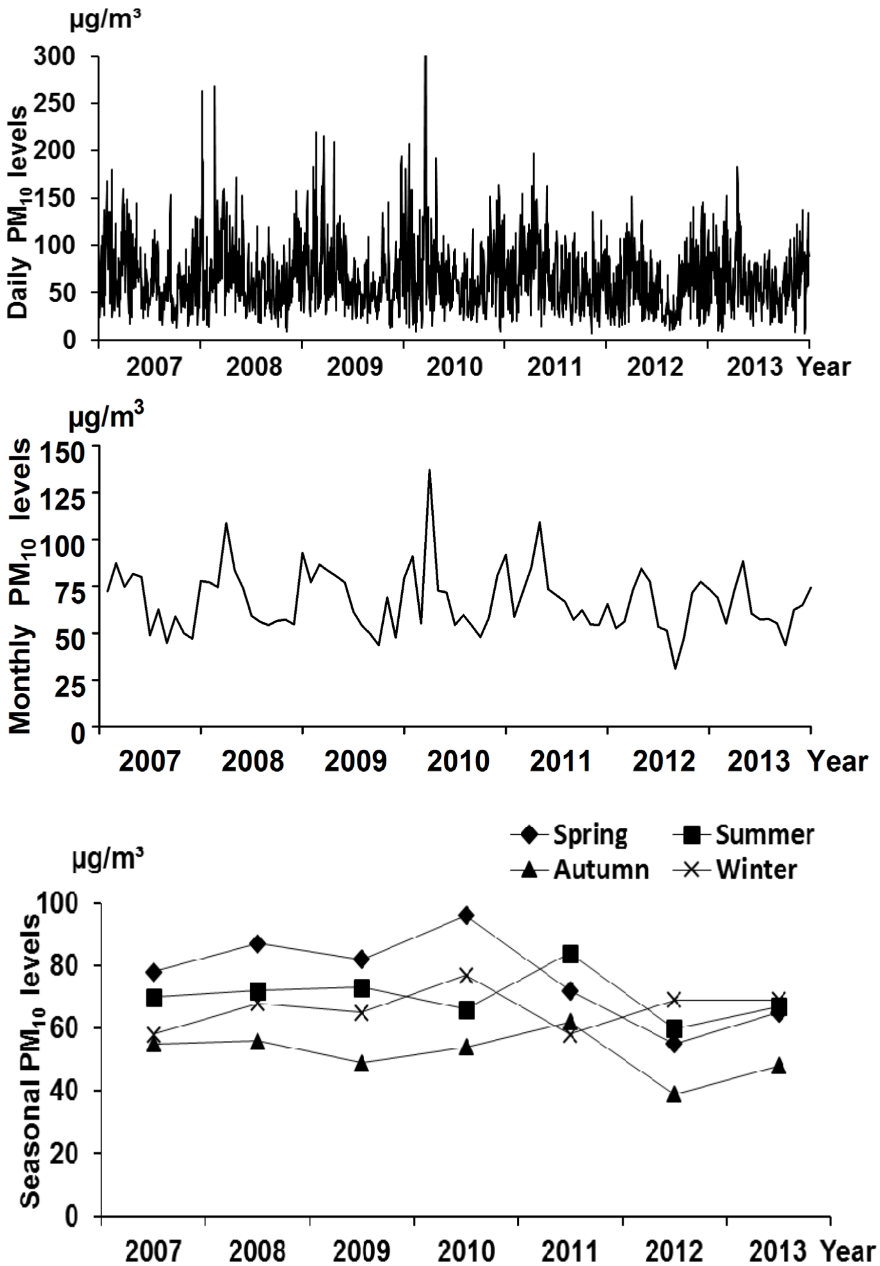

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