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POPULATION BASED COHORT STUDY ON THE ASSOCIATION BETWEEN MATERNAL EXPOSURE TO $PM_{2.5}$ OR LESS DURING PREGNANCY AND FOETAL CONGENITAL ANOMALIES IN KANPUR, INDIA

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ABSTRACT

Few studies from western countries have linked prenatal exposure to ambient particulate matter < 2.5 μm (PM2.5) with increased risk of congenital anomalies. However, the results are mixed. Particularly, evidence is limited for Indian pregnant women. In this retrospective cohort study, we matched the data of all pregnant women laboured in public hospitals during 2020–2022 in Kanpur city and the data of daily average PM2.5, nitrogen dioxide (NO2), sulphur dioxide (SO2) and ozone (O3) concentrations of the nearest monitor station. We calculated a time-dependent exposure over the entire pregnancy for each woman. We used a time varying Cox proportional hazards model to explore the association between PM2.5 exposure and the risk of congenital anomalies, after adjusting for individual confounders and other pollutants. A total of 5000 singleton live births were included in the study, and 530 (1.35%) were with congenital anomalies. An increase of 10 μg/m3 in PM2.5 exposure over the entire pregnancy was significantly associated with increased risk of congenital anomalies, with hazard ratio (HR) of 1.35 [95% confidence interval (95%CI): 1.16, 1.58]. For subtype analyses, PM2.5 exposure exhibited a significant association with cardiac anomalies and other unclassifiable anomalies, with HRs of 1.60 (95%CI: 1.24, 2.08) and 1.42 (95%CI: 1.07, 1.89), respectively. The impacts of PM2.5 exposure on or facial anomalies and musculoskeletal anomalies were not significant. The results indicate high concentration of PM2.5 could increase the risk of congenital anomalies especially for cardiac anomalies. Self-protective measures involving reducing PM2.5 pollution exposure during pregnancy as well as environmental policies aiming to restrict PM2.5 emission could be helpful to reduce the burden of cognitional anomalies.

INTRODUCTION

Over the last two decades, growing epidemiological evidence has suggested that exposure to ambient particulate matters (PM) during pregnancy was associated with adverse birth outcomes such as preterm birth and low birth weight (Li et al., 2017; Wang et al., 2018). Apart from preterm birth and low birth weight, another adverse outcome, known as congenital anomalies or birth defects, also contribute to infant mortality as well as childhood and adult morbidity to a large extent. The latest report of the World Health Organizations showed that there were 303,000 (about 11% of all neonatal deaths) newborns died due to congenital anomalies in 2019 worldwide (World Health Organization, 2019). In addition, congenital anomalies can also con- tribute to long-term disability, which may have significant impacts on individuals, families and societies (World Health Organization, 2010). However, the aetiology of congenital anomalies remains unclear. Pre- natal exposure to air pollution during pregnancy was hypothesized to play a significant role in the incidence of congenital anomalies (Vrijheid et al., 2011).

Studies from the United States, Korea, the United Kingdom and Australia have linked PM with various congenital anomalies, especially for cardiac and orofacial anomalies (Hansen et al., 2009; Kim et al., 2007; Marshall et al., 2010; Rankin et al., 2009; Ritz et al., 2002). However, most previous evidence regarding these associations focusedon the effect of particulate matter < 10 μm (PM10). Compared to PM10, particulate matter < 2.5 μm (PM2.5) has the ability to permeate into circulation, and therefore affect the potential target organ directly (Nelin et al., 2012). PM2.5 has been identified associated with elevated levels of oxidative stress, bulky DNA adducts, chromosome aberrations, micronuclei and DNA methylation in human cord blood and in placenta tissues (Saenen et al., 2017). During pregnancy, foetal experiences rapid cell proliferation, although not fully understood, this alteration in cell level due to maternal PM2.5 exposure during pregnancy may lead to abnormal and disturbed prenatal development, resulting in congenital anomalies (Pedersen et al., 2017).

However, only few studies assessed the association

between PM2.5 exposure during pregnancy and congenital anomalies, with mixed re- sults. Studies in the United States and Spain reported there was no association between PM2.5 exposure and full spectrum of congenital anomalies (Girguis et al., 2016; Marshall et al., 2010; Schembari et al., 2014; Vinikoor-Imler et al., 2013). Agay-Shay et al. reported an inverse association between PM2.5 exposure and patent ductus arteriosus (Agay-Shay et al., 2013). Only one study suggested that PM2.5 exposure was associated with special cardiac anomalies (Padula et al., 2013). In addition, most previous evidences were from the United States, less is known about the associations between PM2.5 and congenital anomalies among Chinese pregnant women. With the rapid urbanization and in- dustrialization, most areas of China are suffering from serious air pol- lution during the last decades. The annual concentrations of PM2.5 in some areas of China were far beyond the air quality guidelines of the World Health Organization (Chen et al., 2018; World Health Organization, 2005). Meanwhile, there were nearly 0.9 million births with congenital anomaly in China per year, and the estimated pre- valence was around 4% to 6% (Dai et al., 2011). Thus, understanding whether exposure to PM2.5 during pregnancy could increase the risk of congenital anomalies or not in China could provide scientific evidence to improve the policies regarding improving air quality and preventing congenital anomalies.

To fill the evidence gap, we collected data of all births laboured in public hospitals during 2020-2022 in Kanpur, an industrial city and collected daily data of PM2.5 concentration during the same period. We aimed to examine the associations between maternal exposure to PM2.5 during pregnancy and the risk of full spectrum of congenital anomalies.

MATERIALS AND METHODS

Study Area and Subjects

The study area was the city of Kanpur with a population of about 3.2 million and is situated in north-central part of India (longitude 88□ 22' E and latitude 26□ 26' N). About 250,000 vehicles ply daily on these roads around the sampling sites. Kanpur has various types of industries such as coal-based 200MW thermal power plant, textiles, leather and leather products and chain. Daily SO2, NOX, PM2.5 and PM10 concentrations for the study area were calculated through 24 hour sampling from six monitoring stations. Local weather data, including temperature and relative humidity, was taken from Air Force Meteorological Station, Chakeri, Kanpur. The average outdoor temperature, relative humidity and wind speed were 30.51 ± 9ºC, 33.27 ± 17.70% and 2.93 ± 1.32 m/s1

We obtained the maternal information and birth outcomes of all the pregnant women who had delivered from Jan 1, 2020 to Dec 31, 2022 in public hospitals of Kanpur city. After excluding women with multiple births, with genetic history of congenital anomalies and without record for gesta- tional length, we finally included 38,961 singleton live births in the study. Maternal information included each pregnant woman's home address, age, nationality, education and parity. Birth outcome information included sex, gestational week, date of labour and diagnosed congenital anomalies.

Definition of Outcomes

According to the system, twenty-three major congenital anomalies (including cleft palate without cleft lip, cleft lip without cleft palate, cleft lip with cleft palate, congenital microtia, other congenital malformations of external ear, talipes equinovarus, polydactyly, syndactyly, limp reduction defects, congenital diaphragmatic hernia, omphalocele, gastroschisis, cardiac anomalies, anencephaly, spina bifida, encephalocele, congenital hydrocephalus, congenital oesophageal atresia, congenital atresia of rectum and anus, hypospadias, extrophy of urinary bladder, conjoined twins, and trisomy 21 syndrome) were recorded in detail by physicians in each hospital, while other unclassifiable types of congenital anomalies were classified as “others” (Xie et al., 2016). Similar to a previous study (Girguis et al., 2016), we further classified the twenty- four types (including those classified as others) of congenital anomalies into 4 subgroups in our study: 1) orofacial anomalies (including cleft palate without cleft lip, cleft lip without cleft palate, cleft lip with cleft palate, congenital microtia and other congenital malformations of ex- ternal ear); 2) musculoskeletal anomalies (including talipes equino- varus, polydactyly, syndactyly, limp reduction defects, congenital dia- phragmatic hernia, omphalocele and gastroschisis); 3) cardiac anomalies; and 4) other unclassifiable anomalies (including anence- phaly, spina bifida, encephalocele, congenital hydrocephalus, con- genital oesophageal atresia, congenital atresia of rectum and anus, hypospadias, extrophy of urinary bladder, conjoined twins, trisomy 21 syndrome and other unspecific congenital anomalies) (Girguis et al., 2016).

Exposure Assessment

We estimated each pregnant woman's exposure by using the nearest monitor approach. Briefly, the data of daily average concentrations of PM2.5, nitrogen dioxide (NO2), sulphur dioxide (SO2) and ozone (O3) from each monitoring station in Kanpur city was obtained from the IMD. There were 6 monitoring stations and we matched each pregnant woman's home address to the nearest monitoring station. The majority (80%) of participants lived within 10 km from the nearest monitors. Then we assessed each woman's moving average exposure to PM2.5, NO2, SO2 and O3, respectively, during the entire pregnancy for each week, based on the date of last menstrual period (LMP) and the date of delivery.

Statistical Analysis

Given the variability among exposure length (gestational week) of each birth, we fitted a Cox proportional hazards model with time de- pendent exposure to explore the associations between PM2.5 exposure over the entire

pregnancy and the risk of congenital anomalies. In the model, gestational age was fitted as time scale, and in each week, a woman could either remain pregnant or give birth to an infant with congenital anomalies (defined as event) or not (defined as censoring). We calculated a time-dependent exposure for each woman following previous studies (Hao et al., 2016; He et al., 2016; Slama et al., 2014). Briefly, given a birth with gestational age for t weeks, we broke it into t time intervals, with one row of data for each interval. We calculated the average exposure to pollutants for each of the intervals, and assigned the status with event or censoring. Then we estimated the effect of the exposure during the whole pregnancy period on the risk of congenital anomalies.

In order to examine proportional hazard assumption and potential trend of the hazard risk over gestational age, we estimated the time varying HRs of each week with time-varying coefficient models by adding an interaction of time variable with exposure. To find the cause specific effects, we also fitted the full adjusted model for each subgroup of congenital anomalies, respectively. All statistical analyses were conducted using R, version 3.4.4 (RCore Team). The "survival" package was used to perform Cox propor- tional hazards model. All statistical tests were two-sided and a p value < 0.05 was considered as statistical significance.

RESULTS

There was a total of 9000 births delivered from Jan 1, 2020 to Dec 31, 2022 in the study. Among these births, 530 (1.35%) had congenital anomalies. Table 1 shows the characteristics of pregnant women and children. Most pregnant women were aged 25 to 29 years, with ethnic Han and were nulliparous. Pregnant women with an older age (≥35 years), being other ethnic minorities, having educational time for 10 to 12 years (high school) and being nulliparous demonstrated a high risk of congenital anomalies ($p < 0.05$ for Chi-square test). The mean concentrations of PM2.5, NO2, SO2 and O3 over the entire pregnancy for all participants were 50.07 µg/m, 39.40 µg/m, 73.17 µg/m, 86.97 µg/m3, respectively.

Table 1: Characteristics of the study population and the distribution of pregnancy exposures.

Variable	Cases	Congenital anomalies (%)	Mean concentration during pregnancy (µg/m³)			
			PM	NO	SO	O
Age						
< 25	883	1.02	49.3	39.8	75	87.4
25–29	1770	50.2	39.3	72.7	72.7	86.8
30–34	4227	1.48	50.4	39.3	72.7	86.7
≥35	2506	2.08	50.2	39.4	72.9	87.4
Educational Qualification						
≤9	535	0.26	49.7	40.5	77.9	86.7
10-12	4156	2.39	50.1	39.7	75	86.6
> 12	4695	1.66	50.3	38.6	69.5	87.3
Gestational weeks						
< 28	263	65.78	49.2	36.9	62.5	93
28-32	647	4.64	50.3	38.9	72	87.2
32-37	6354	1.52	49.9	39.4	72.9	87.2
> 37	2122	0.76	50.1	39.4	73.3	86.9
Baby's sex						
Male	3120	1.42	50.1	39.4	73.3	87
Female	6266	1.13	50.1	39.4	73.1	87
Overall	9386	1.35	50.1	39.4	73.2	87

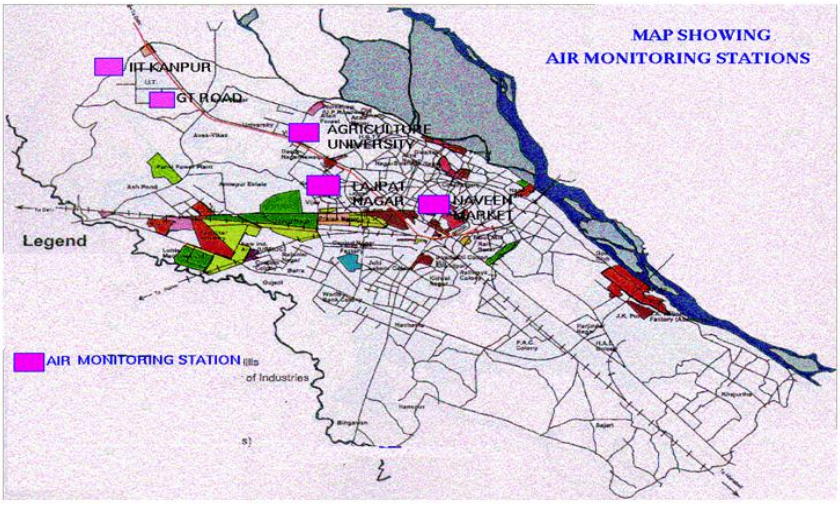

Figure 1: Air Monitoring Stations in Kanpur, India.

Fig. 2 show the unadjusted and adjusted associations between PM2.5 exposure over the entire pregnancy and the risk of congenital anomalies. In the crude model, we found PM2.5 exposure over the entire pregnancy was related to congenital anomalies, while the association was not significant, with a HR of 1.05 (95%CI: 0.96, 1.16). In the model adjusted for individual characteristics, a 10 µg/m3 increase in PM2.5 exposure over the entire pregnancy was marginally associated to increased risk of congenital anomalies, with a HR of 1.10 (95%CI: 1.00, 1.22). When we included NO2, SO2 or O3 respectively, we found sig- nificant associations between PM2.5 exposure and the risk of congenital anomalies, with HRs ranged from 1.24 (adjusted for O3) to 1.40 (ad- justed for NO2). In the full adjusted model, we found a 10 µg/m3 in- crease in PM2.5 exposure over the entire pregnancy was significantly associated with increased risk of congenital anomalies, with a HR of1.35 (95%CI: 1.16, 1.58).

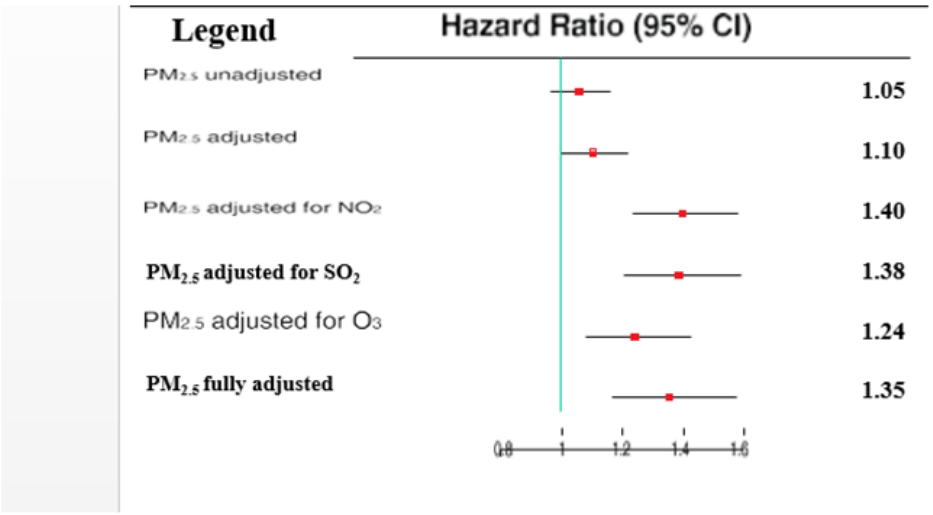

Figure 2: Hazard ratios (and 95% confidence intervals) of all congenital anomalies, associated with a 10 µg/m3 increase in PM2.5 exposure during entire pregnancy in unadjusted and adjusted models.

Fig. 3 shows the estimated effects of PM2.5 exposure on the risk of congenital anomalies with a time-varying coefficients model. The proportional hazards assumption was satisfactory when performed Schoenfeld residuals check (p = 0.47). The pregnant women at early gestation probably appear to be more sensitive to PM2.5 exposure than later gestations.

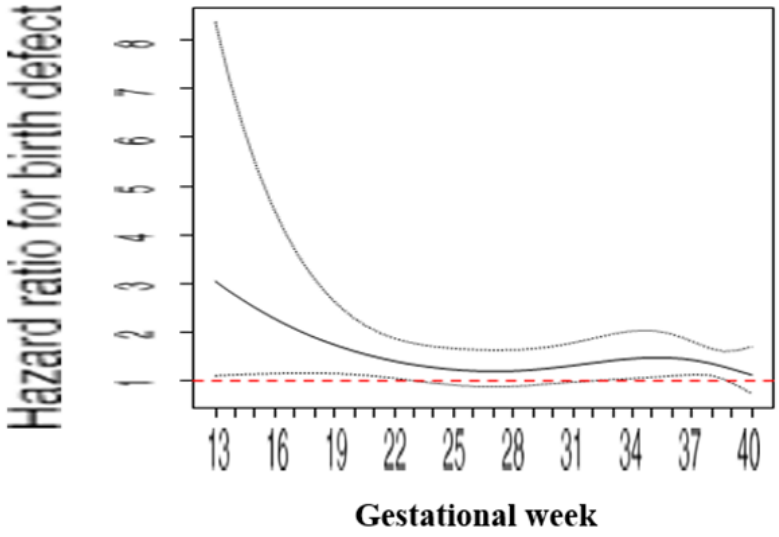

Figure 3: Hazard ratios (and 95% confidence intervals) of all congenital anomalies, associated with a 10 µg/m^3 increase in moving average $PM_{2.5}$ exposure for each gestational week.

Fig. 4 provides the associations between PM2.5 exposure and the risks for each subgroup of congenital anomalies. We found a 10 µg/m3 increase in PM2.5 exposure over the entire pregnancy was significantly associated with

increased risk of cardiac anomalies and other unclassifiable anomalies, with HRs of 1.60 (95%CI: 1.24, 2.08) and 1.42 (95%CI: 1.07, 1.89), respectively. PM2.5 exposure over the entire pregnancy was related to increased risks of orofacial anomalies and musculoskeletal anomalies, but not statistically significant.

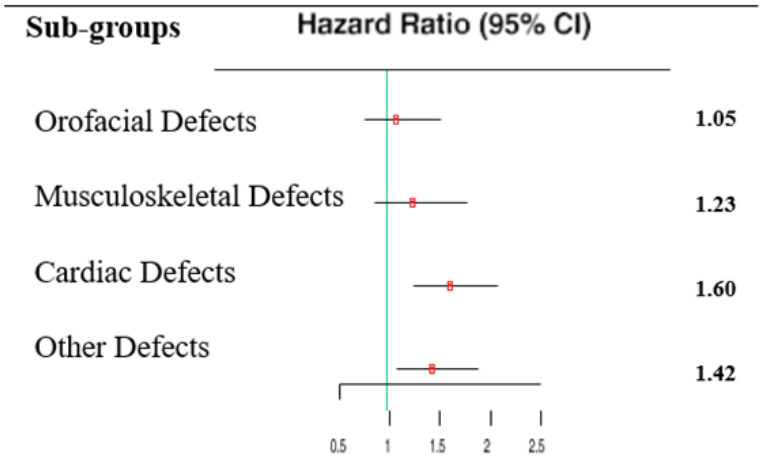

Figure 4: Hazard ratios (and 95% confidence intervals) of congenital anomalies by subgroups associated with a 10 μg/m^3 increase in $PM_{2.5}$ exposure during entire pregnancy.

DISCUSSION

In this study, we analysed the birth outcomes of pregnant women who had delivered babies during 2015 to 2016 in Yinchuan city, and found that maternal exposure to PM2.5 over the entire pregnancy was significantly associated with increased risk of congenital anomalies while adjusting for individual characteristics and other pollutants, with a HR of 1.35 (95%CI: 1.16, 1.58) for each 10 μg/m3 increase in PM2.5.

We also found cardiac anomalies were more sensitive to the PM2.5 ex- posure than orofacial and musculoskeletal anomalies. To our best knowledge, this is the first study providing evidence that exposure to PM2.5 during pregnancy were associated to the increased risk of cognitional anomalies in pregnant women. The associations between perinatal PM2.5 exposure and the risk of congenital anomalies reported in our study was consistent with a previous study conducted in California. Padula et al. found in a Californian case-control study with 822 cases that, PM2.5 exposure during the first two months of pregnancy was associated with special subtype of cardiac anomies, with an odds ratio (OR) of 2.6 (95%CI: 1.1, 6.5) for the highest quartile (14.8–26.1 μg/m3) compared with the lowest quartile (3.6–11.0 μg/m3) of exposure. Nevertheless, for other subtype of cardiac anomalies, they did not find a significant association (Padula et al., 2013). In contrary, studies from Massachusetts, the United States and Barcelona, Spain reported there were no association between perinatal PM2.5 exposure and full spectrum of congenital anomalies (Girguis et al., 2016; Schembari et al., 2014). The inconsistent findings could be caused by the difference in participants, exposure assessment, and statistical methods. Due to the paucity of epidemiological evidence, it is hard to make a conclusion at this stage, and further studies are still needed.

We classified the twenty-four types of congenital anomalies into 4 subgroups in order to reduce the massive comparisons in testing all the 24 congenital anomaly subtypes and insure the sufficient numbers of cases for model convergence (Schembari et al., 2014). We found that only cardiac and other unclassifiable anomalies were associated with perinatal PM2.5 exposure, while the effects on orofacial and musculoskeletal anomalies were not significant. Most previous studies sup- ported that cardiac anomalies could be impacted by perinatal PM2.5 exposure consistently, while the evidence for other anomalies were more disharmonious (Jin et al., 2015; Vrijheid et al., 2011). The possible mechanism underlying the effects of prenatal PM2.5 exposure on the risk of congenital anomalies is still unclear, as there could be multifactorial aetiology and different types of anomalies likely to have very distinct aetiology (Schembari et al., 2014). Studies suggested that air pollution could induce oxidative stress during pregnancy (Kannan et al., 2006). Oxidative stress impacts the transportation of oxygenation and nutrients from mother to the foetus and may affect organogenesis and neural crest cell migration and differentiation, which plays an important role in heart development (Schembari et al., 2014). The procedure may contribute to the risk of cardiac anomalies associated with PM2.5 exposure. More studies are needed to examine the reason for the null effect on orofacial and musculoskeletal anomalies. In this study, we also noticed that pregnant women at early gestation appeared to be more sensitive to PM2.5 exposure than later gestations. Given the cardiovascular system is developed during early pregnancy, and the time window of cardiac development is differ from orofacial and musculoskeletal development, it may contribute to

the difference be- tween the PM-associated effects on cardiac anomalies and orofacial and musculoskeletal anomalies. However, more studies are needed.

A notable strength of our study is that, we examined the full spectrum as well as several subgroups of congenital anomalies based on the cohort design of all singleton live births in public hospital of Kanpur. Most studies used a case-control design, selecting cases from clinical or autopsy reports, and investigated cardiovascular anomalies only, which may restrict the understanding of the integrated relationship between air pollution and congenital anomalies (Chen et al., 2014). The relatively large number of births in our study also helped to reduce the uncertainties due to random misclassification. Another advantage of the study lies in the application of a time dependent exposure with a Cox proportional hazard model to estimate the association of PM2.5 exposure during pregnancy and congenital anomalies (Hao et al., 2016). Amounts of previous studies treated the average concentration of pollutants over the entire pregnancy as a time independent variable and then estimated the associations with logistic models (Chen et al., 2014). As births with congenital anomalies may have shorter gestational weeks than normal births, failing to consider the difference in length of exposure time may distort the effect estimates.

There were also several limitations. We evaluated each pregnant woman's PM2.5 exposure based on the nearest monitor station. There could be certain exposure misclassification due to the disparity of distances of each participant to the monitor station as we did not calculate distance-weight exposure due to the lack of the exact address which could be geocoded (Chen et al., 2014). We didn't capture indoor air pollution level and maternal time-activity patterns, so cannot preclude that some dilution of the 'true' effects has occurred due to exposure misclassification. In addition, we can't identify the specific component of PM2.5 which cause the increased risk of congenital anomalies, as the data on PM2.5 components were unavailable. Further studies investigating PM components and their sources are warranted. Several factors including smoking, alcohol consumption, medicine usage and occupational exposures might be potential risk factors for congenital anomalies (Chen et al., 2014). We were unable to consider them as co- variables because they were not adequately recorded for all participants. However, previous study has indicated that there was little impact of maternal smoking on the association between air pollution and congenital anomalies among Spanish (Schembari et al., 2014). We only identified 3 (0.56%) women who delivered a baby with congenital anomalies that consumed alcohol during pregnancy. Therefore, the limitation can hardly distort the effect estimates. Lastly, as an observational study, we cannot establish the causal association between PM and congenital anomalies.

CONCLUSION

PM2.5 exposure over the entire pregnancy was significantly associated with an increased risk of congenital anomalies. Cardiac anomalies were more sensitive to the PM2.5 exposure than orofacial and musculoskeletal anomalies. Public health policy should be implemented to reduce PM2.5 pollution and self-protective measures such as wearing a mask or using air puffier during pregnancy could be helpful to lessen the burden of cognitional anomalies.

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