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Early life exposure to particulate matter air pollution (PM_1, $PM_{2.5}$ and PM_{10}) and autism in Shanghai, China: A case-control study

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ABSTRACT

Background: The evidence for adverse effects of ambient particulate matter (PM) pollution on mental health is limited. Studies in Western countries suggested higher risk of autism spectrum disorder (ASD) associated with PM air pollution, but no such study has been done in developing countries.

Methods: A case-control study was performed in Shanghai with a multi-stage random sampling design. Children's exposures to PM_1, $PM_{2.5}$ and PM_{10} (particulate matter with aerodynamic diameter $< 1\,\mu m$, $< 2.5\,\mu m$ and $< 10\,\mu m$, respectively) during the first three years after birth were estimated with satellite remote sensing data. Conditional logistic regression was used to examine the PM-ASD association.

Results: In total, 124 ASD cases and 1240 healthy controls were included in this study. The median levels of PM_1, $PM_{2.5}$ and PM_{10} exposures during the first three years of life were 48.8 $\mu g/m^3$, 66.2 $\mu g/m^3$ and 95.4 $\mu g/m^3$, respectively, and the interquartile range (IQR) for these three pollutants were 4.8 $\mu g/m^3$, 3.4 $\mu g/m^3$ and 4.9 $\mu g/m^3$, respectively. The adjusted odds ratios (and 95% confidence intervals) of ASD associated with an IQR increase for PM_1, $PM_{2.5}$ and PM_{10} were 1.86 (1.09, 3.17), 1.78 (1.14, 2.76) and 1.68 (1.09, 2.59), respectively. Higher ORs of ASD associated with PM pollution were observed in the second and the third year after birth.

Conclusions: Exposures to PM_1, $PM_{2.5}$ and PM_{10} during the first three years of life were associated with the increased risk of ASD and there appeared to be stronger effects of ambient PM pollution on ASD in the second and the third years after birth.

1. Introduction

Air pollution is a significant global issue that has remarkably contributed to increasing burden of disease over the past decades, especially in low and middle-income countries (Cohen et al., 2017). Numerous studies have investigated the associations between exposure to outdoor air pollution and a wide range of diseases, including cardiovascular and respiratory diseases, lung cancer, infectious disease and adverse birth outcomes (Chen et al., 2017b; Kampa and Castanas, 2008; Shah et al., 2011). In contrast to the well-established relationships between air pollution and cardiovascular and pulmonary diseases, the effect of air pollution on mental health is still not clear (Genc et al., 2012). A handful of previous studies have reported that the increased risk of mental health outcomes were associated with ambient air pollution, including autism and cognitive development in children, depression in elderly and anxiety in pregnant women (Becerra et al., 2013; Freire et al., 2010; Lim et al., 2012; Power et al., 2015).

Exposure to ambient particulate matter (PM) can affect neonatal

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immune system and cognitive abilities (Currie et al., 2009; Hansen et al., 2008). Studies in Western countries have found that exposure to PM air pollution was associated with children's mental health, including autism spectrum disorder (ASD), a group of serious developmental disorders in children (Becerra et al., 2013; Volk et al., 2013). Most of previous studies on air pollution and ASD focused on prenatal exposure to air pollution. However, whether post-natal exposure to air pollution increases the risk of ASD is not clear. Another study in the U.S. reported the significant association of maternal exposure to air pollution and ASD, and a weaker association between 9-month post-natal exposure and ASD (Raz et al., 2015). In addition, no such study has been done in developing countries. Moreover, most of studies on health effects of PM focused on $PM_{2.5}$ and PM_{10} (particulate matter with aerodynamic diameter $< 2.5\,\mu m$ and $10\,\mu m$, respectively), but evidence for health effects of smaller particles, such as PM_1 (particulate matter with aerodynamic diameter $< 1\,\mu m$) which is a major component of $PM_{2.5}$, is very limited (Kan, 2017; Wang et al., 2018).

In this study, we examined the associations between exposures to three air pollutants (PM_1, $PM_{2.5}$ and PM_{10}) during the first three years of life and ASD in Shanghai, China, with a case-control design.

2. Methods

2.1. Study design

A cross-sectional study was conducted to assess child development and its influencing factors in Shanghai (population 24,197,000 and area 6340 km^2), China, in June 2014. The study design and sampling method were previously reported (Chen et al., 2016; Jin et al., 2018). Briefly, a multi-stage random sampling design, stratified by district, was used to select children at kindergartens (aged 3–6 years) and primary schools (aged 7–12 years). In general, children take pre-primary education between 3 and 6 years old in kindergartens and primary education between 7 and 12 years old in primary schools in China. Firstly, 7 districts including 3 urban districts (Yangpu, Xuhui, and Jing'an) and 4 suburb districts (Minhang, Pudong, Fengxian, and Chongming) were randomly selected from 17 districts in Shanghai. Then, in each selected district, 15% of kindergartens and primary schools were randomly selected. As children from special education schools are at high risk of ASD, all special education schools in the 7 districts were investigated in this survey. Finally, all children in selected kindergartens, primary schools and special education schools were investigated. In total, 84,934 children aged 3–12 years from 96 kindergartens, 55 primary schools and 28 special education schools participated in this study. The locations of these schools are shown in Fig. 1.

2.2. ASD diagnosis and control selection

Firstly, all children involved in this study took the ASD screening, and then, suspected cases were further confirmed by experienced paediatricians. In the first stage, parents of these children were required to complete the Social Communication Questionnaire (SCQ) for ASD case screening (Schanding et al., 2012). Children with total score of SCQ ≥ 15 were regarded as suspected cases of ASD (Berument et al., 1999), and in the second stage, teachers of these children at kindergarten or school were required to complete the SCQ again to confirm the results. In this stage, 10% of children with inconsistent results (positive results from parents and negative results from teachers) were randomly selected and further interviewed by two paediatric specialist. As the result of it, the false negative rate was 1.2/10,000.

In the third stage, suspected cases (711 children with positive results of screening from both their parents and teachers) took an interview by paediatric specialist in developmental behaviour from Xinhua Hospital, Shanghai. Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and Wechsler Intelligence Scale for Children-Revised (WISC-R) were used for developmental evaluation of children $<$ 6 years and ≥6 years, respectively (Wechsler, 1967, 1974). All ASD cases were diagnosed by paediatricians according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM−V) (American Psychiatric Association, 2013). Each suspected case was interviewed by two paediatricians independently. If inconsistent diagnoses by two different paediatricians occurred, it was determined by the third experienced paediatrician. Details of case selection are shown in Fig. 2. As all children in this study were between the ages of 3 and 12 by the time they were investigated and autism is a disorder that begins in infancy (during the first three years of life) (Lord et al., 2000), participants' past exposures to PMs should be linked with their outcomes. Thus, this study was conducted with a case-control design. Controls were selected from healthy children identified in this cross-sectional study who were screened negative by both parents and teachers. Eligible controls are children from normal schools that have no mental health problems, history of any mental disease or disabilities revealed in this survey. We randomly selected 10 controls for each ASD case matched by age and sex without replacement (Becerra et al., 2013). The criteria for case confirmation and control selection were the same in all selected districts of Shanghai.

2.3. Exposure assessment

Daily concentrations of PM_1, $PM_{2.5}$ and PM_{10} in Shanghai during the study period were estimated at a resolution of 0.01 degree (≈1 km) using a machine learning method (random forests model) with ground monitoring concentration, satellite-retrieved aerosol optical depth (AOD), meteorological data, land cover data and the information on other spatial and temporal predictors. Ground measured PM_1 data were obtained from 77 stations of China Atmosphere Watch Network (CAWNET). Ground measured $PM_{2.5}$ and PM_{10} data were obtained from 1497 stations of China National Environmental Monitoring Center (CNEMC). Details of data processing and data sources were previously reported (Chen et al., 2017a; Chen et al., 2018). Model development and validation are shown in the Supplementary Material. Briefly, the results of 10-fold cross-validation (CV) showed the CV R^2 for annual average of predicted PM_1 was 75%. Those for $PM_{2.5}$ and PM_{10} were 86% and 81%, respectively. As ASD is a disorder that usually begins within the first three years of life (Lord et al., 2000), we estimated participants' mean exposures to three pollutants during first three years of life, according to their home addresses and dates of birth. As the satellite-based prediction cover the time period during 2005–2016, ASD cases and controls who were born after 2005 and provided complete geolocation information were included in this study.

2.4. Statistical analyses

Conditional logistic regression models were used to estimate the associations between exposure to PMs and ASD. A range of risk factors of ASD and potential confounders were considered according to previous studies (Bhasin and Schendel, 2007; Guinchat et al., 2012; Raz et al., 2015). We adjusted for a range of potential confounders in the model, including birth weight, gestational weeks, disease history (serious diseases, e.g., jaundice, encephalitis and epilepsy), trauma history, maternal age, familial mental health history, parents' marital status, parental relationship, parenting, income, parents' educational level and smoking status. To examine the robustness of results, sensitivity analyses were performed. The variable of district (as a random-effect term) and district-level GDP per capital were included in the model to control for the potential spatial clustering and neighbourhood-level social economic status, respectively. The associations between PMs and ASD were expressed as odds ratio (OR) and 95% confidence intervals (95% CI) associated with an interquartile range (IQR) increase in each pollutant. All analyses were performed with R software version 3.4.0. Conditional logistic regression was conducted with “survival” package.

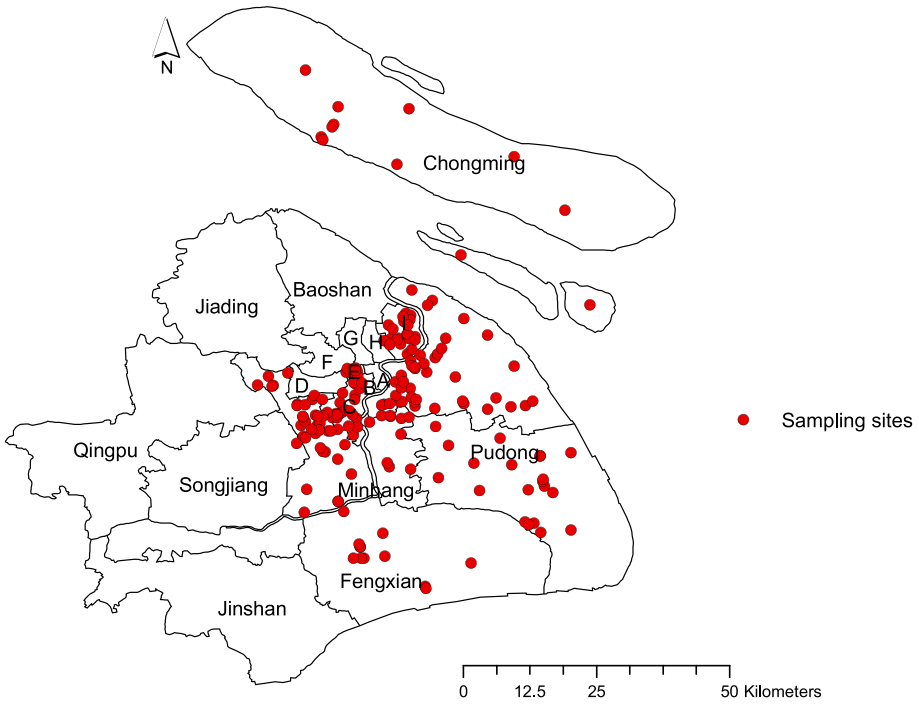

Fig. 1. Locations of sampling schools in Shanghai.
*A: Huangpu; B:Luwan; C: Xuhui; D: Changning; E: Jing'an; F: Putuo; G: Zhabei; H: Hongkou; I: Yangpu.

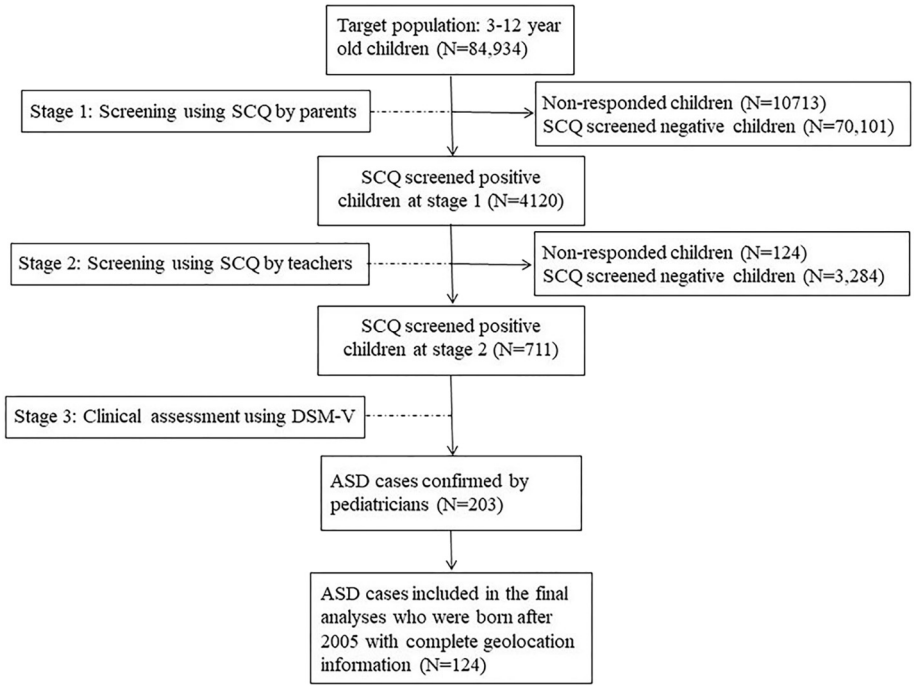

Fig. 2. Flow chart of case selection.

3. Results

In total, 124 ASD cases and 1240 healthy controls were included in this study. Table 1 shows the demographic and prenatal characteristics of cases and controls. More male cases (77%) were identified than female cases (23%). The mean age of cases was 7 years old. ASD cases were more likely to have disease history (e.g., neonatal jaundice, meningitis and fever convulsions) and trauma history (e.g., natural disaster, serious accident and violence) than controls. In addition, family members of ASD cases were more likely to have mental health problems. Other sociodemographic and prenatal variables were evenly distributed in cases and controls.

Table 2 indicates participants' estimated exposures to PM_1, $PM_{2.5}$ and PM_{10} during the first three years after birth. The exposure levels of cases to the three pollutants were slightly higher than controls. The IQRs for PM_1, $PM_{2.5}$ and PM_{10} exposures during the first three years of life were 4.8 $\mu g/m^3$, 3.4 $\mu g/m^3$ and 4.9 $\mu g/m^3$, respectively. The mean exposures of cases to PM_1, $PM_{2.5}$ and PM_{10} during the study period were

Table 1
Demographic and prenatal characteristics of cases and controls.

Characteristics	Cases		Controls		χ^2	p
	n	%	n	%		
Sex					–	–
Male	96	77%	960	77%		
Female	28	23%	280	23%		
School					–	–
Primary school	6	5%	–	–		
Kindergarten	54	44%	567	46%		
Special education schools	64	52%	673	54%		
Age (mean + SD)	6.9	1.8	6.9	1.8	–	–
Birth weight					3.3	0.19
≤2500 g	6	5%	57	5%		
2500–4000 g	110	89%	1035	83%		
≥4000 g	8	6%	148	12%		
Gestational weeks					5.3	0.07*
< 37	13	10%	69	6%		
37–42	105	85%	1124	91%		
> 42	6	5%	47	4%		
Disease history					52.1	< 0.01
Yes	53	43%	198	16%		
No	71	57%	1042	84%		
Trauma history					6.5	0.01*
Yes	9	7%	33	3%		
No	115	93%	1207	97%		
Maternal age (years)					10.1	< 0.01
≤25	22	18%	390	31%		
25–34	95	77%	788	64%		
≥35	7	6%	62	5%		
Familial mental health history					10.4	< 0.01*
Yes	7	6%	16	1%		
No	117	94%	1224	99%		
One-parent family					0.05	0.83
Yes	7	6%	59	5%		
No	117	94%	1181	95%		
Parental relationship					3.3	0.07
Good	113	91%	1182	95%		
Poor	11	9%	58	5%		
Parenting					17.1	< 0.01*
Permissive	31	25%	152	12%		
Authoritative	3	2%	57	5%		
Neglectful	6	5%	47	4%		
Others	84	68%	984	79%		
Annual income					3.5	0.32
< 30,000	21	17%	143	12%		
30,000–100,000	41	33%	473	38%		
100,000–200,000	40	32%	396	32%		
> 200,000	22	18%	228	18%		
Educational level of dependents					0.37	0.83
Illiteracy and primary education	10	8%	90	7%		
Secondary education	55	44%	584	47%		
Tertiary education	59	48%	566	46%		
Parents' smoking status					2.9	0.09
Smoker	75	60%	646	52%		
Non-smoker	49	40%	594	48%		
Total	124	100%	1240	100%		

Note: Cases and controls were matched by sex and age.
* p values of Fisher's Exact Test.

48.3 μg/m^3, 66.7 μg/m^3 and 96.1 μg/m^3, respectively, while those for controls were 47.8 μg/m^3, 66.2 μg/m^3 and 95.3 μg/m^3, respectively. The correlation of participants' exposures to PM_1 and $PM_{2.5}$ was 0.71 ($p < 0.01$) and that of $PM_{2.5}$ and PM_{10} was 0.80 ($p < 0.01$). The ratios of PM_1 to $PM_{2.5}$ and $PM_{2.5}$ to PM_{10} were 0.80 and 0.69, respectively. Detailed summaries of participants' exposures to three pollutants during the exposure period are shown in Table S1-S3 in Supplementary Material.

The ORs and 95% CIs of ASD associated with an IQR increase in each pollutant are shown in Fig. 3. Exposures to PM_1, $PM_{2.5}$ and PM_{10} during the first three years of life significantly increased the risk of ASD. The crude ORs (and 95% CIs) for PM_1, $PM_{2.5}$ and PM_{10} were 1.50 (1.05, 2.15), 1.56 (1.13, 2.17) and 1.51 (1.10, 2.07), respectively. After controlling for potential confounders, the adjusted ORs (and 95% CIs) for the three pollutants were 1.86 (1.09, 3.17), 1.78 (1.14, 2.76) and 1.68 (1.09, 2.59), respectively.

Table 2
Summary of participants' exposure to air pollutants (μg/m^3) during the first three years of life.

Pollutants	Mean	Min	Percentile			Max	p*
			25th	50th	75th		
PM_1							0.046
Case	48.3	40.4	45.8	48.2	50.5	58.9	
Control	47.8	41.8	44.9	47.2	50.5	59.1	
All participants	48.8	40.4	45.7	48.1	50.5	59.1	
$PM_{2.5}$							0.013
Case	66.7	60.2	65.5	66.6	68.0	72.2	
Control	66.2	57.9	64.5	66.0	68.0	72.4	
All participants	66.2	57.9	64.6	66.0	68.0	72.4	
PM_{10}							0.030
Case	96.1	86.0	94.6	96.7	98.1	100.9	
Control	95.3	85.8	92.9	96.1	98.0	101.0	
All participants	95.4	85.8	93.1	96.2	98.0	101.0	

* p value of Mann-Whitney U test for distribution differences between cases and controls.

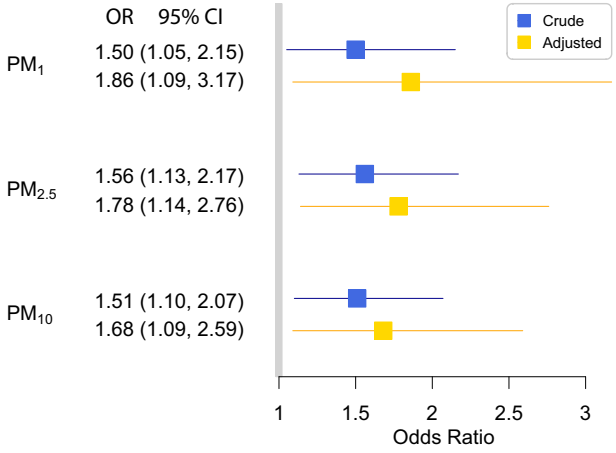

Fig. 3. The ORs and 95% CIs of ASD associated with an interquartile range increase in PM_1, $PM_{2.5}$ and PM_{10} during the first three years after birth. Note: Crude model only controlled sex and age by matched design and adjusted model controlled for birth weight, gestational weeks, disease history, trauma history, maternal age, familial mental health history, parents' marital status, parental relationship, parenting, income, parents' educational level and smoking status.

The effects of PM_1, $PM_{2.5}$ and PM_{10} on ASD in each single year after birth were also evaluated and the results are shown in Table 3. Stronger associations between air pollutants and ASD were present in the second

Table 3
Adjusted IQR ORs and 95% CIs of ASD associated with exposures to three pollutants in each single year of their early lives.

Pollutants	1st year (age 1)		2nd year (age 2)		3rd year (age 3)	
	OR	95% CI	OR	95% CI	OR	95% CI
PM_1	1.61	(0.96, 2.70)	1.78	(1.06, 3.00)	1.87	(1.11, 3.15)
$PM_{2.5}$	1.07	(0.80, 1.43)	1.50	(1.01, 2.22)	1.78	(1.05, 3.02)
PM_{10}	1.16	(0.91, 1.49)	1.73	(1.11, 2.68)	1.58	(0.98, 2.56)

Note: Models controlled for birth weight, gestational weeks, disease history, trauma history, maternal age, familial mental health history, parents' marital status, parental relationship, parenting, income, parents' educational level and smoking status.

(age 2) and third years (age 3) than the first year (age 1). Exposure to air pollutants in the first year after birth was not significantly associated ASD [IQR ORs and 95% CIs for PM_1, $PM_{2.5}$ and PM_{10} were 1.61 (0.96, 2.70), 1.07 (0.80, 1.43) and 1.16 (0.91, 1.49), respectively]. The IQR ORs and 95% CIs for PM_1, $PM_{2.5}$ and PM_{10} in the second year were 1.78 (1.06, 3.00), 1.50 (1.01, 2.22) and 1.73 (1.11, 2.68), respectively, and those for the third year were 1.87 (1.11, 3.15), 1.78 (1.05, 3.02) and 1.58 (0.98, 2.56), respectively. The results of sensitivity analyses showed the results did not substantially change after controlling for potential spatial clustering and neighbourhood-level social economic status (Table S4 in the Supplementary Material).

4. Discussion

In this study, we estimated the individual exposures to ambient PM_1, $PM_{2.5}$ and PM_{10} of 124 ASD cases and 1240 controls during the first three years after their births. Then, we examined the associations between exposures to the three air pollutants and ASD using conditional logistic regression. We found significantly increased risk of ASD associated with exposures to PMs during the first three years of life. Stronger effects of PM were observed for the second and third year exposures.

This is the first study to examine the effects of long-term exposure to PM air pollution on ASD during the early life of children in China. Previous studies conducted in the U.S. have reported increased risk of ASD associated with air pollution. A nested case-control study in the U.S. found exposure to $PM_{2.5}$ during pregnancy and 9 months before and after pregnancy were associated with increased risk of ASD [ORs associated with per 4.42 $\mu g/m^3$ increase in $PM_{2.5}$ and 95% CIs were 1.50 (1.16, 1.94), 1.32 (1.04, 1.69) and 1.29 (1.00 1.67), respectively] (Raz et al., 2015). Another study in Los Angeles county found 12–15% increase in odds of ASD associated with per 4.68 $\mu g/m^3$ increase in $PM_{2.5}$ (Becerra et al., 2013). Our results were consistent to those previous studies, even though we used different assessments of exposure, as our study was focused on children's exposure to PM in their first three years of lives.

The causes of autism are complex and have not been fully understood. In addition to genetic and familial factors, the contribution of environmental factors has been increasingly recognized (Landrigan, 2010). PMs are a complex mixture of solid and liquid particles and its toxic components have been recognized to cause adverse health outcomes (Schlesinger, 2007). However, the developing brains of school children are more vulnerable to such toxic exposures in the environment (Cho et al., 2010). There are several potential mechanisms explaining our findings: Firstly, exposure to PM air pollution may have an effect on immune system of new births through reducing T cells and increasing B lymphocytes in cord blood of newborns (Hertz-Picciotto et al., 2005), and the disrupted immune system and neuro-inflammation have been linked with ASD (Careaga et al., 2013; Gadad et al., 2013). Studies examining biomarkers also indicated the systematic inflammation and oxidative stress had impacts on the pathogenesis of ASD (Ashwood et al., 2008; Li et al., 2009). Secondly, a study in Mexico City found exposure to air pollution could damage prefrontal cortex of children, which might be related to their cognitive dysfunction (Calderón-Garcidueñas et al., 2008). Finally, toxicological studies reported constituents of PM including polycyclic aromatic hydrocarbons and diesel exhaust particles had impacts on brain activity and function (Hougaard et al., 2008; Perera et al., 2006). Air pollution might interact with MET receptor tyrosine kinase gene, an important gene for neurodevelopment during early life, to increase the risk of ASD (Volk et al., 2014).

We found stronger associations between PM pollution and ASD during the second and third years after birth, which might be associated with some critical periods of child development. For example, the period from 6 to18 months are critical to develop the core attachment to parents and the period from 12 to 30 months are critical for their linguistic and intellectual development (Sylva, 1997). The period between 2 and 4 years after birth is important for the development of neural wiring patterns, which is relevant to the children's development of abilities to interact and communicate with others (Courchesne et al., 2007). Considering babies breathe air by themselves after birth, air pollution may have adverse effects on their health more directly and significantly. As babies grow older, they breathe more air, which means they may expose to more air pollution during the second and third years after birth than the first year. Epidemiological studies showed a consistent male-to-female ratio among ASD cases of about 4:1 (Fombonne, 2003). However, the ratio in our study was 3.3. The discrepancy may be due to diagnostic approaches, as different symptom profiles were observed among boys and girls who exceeded the cutoff (Constantino and Charman, 2012). Other factors, such as paternal age, can also affect the ratio (Anello et al., 2009). Modest variations in annual concentrations of PMs during the exposure period were observed. We found the changes of concentrations of PMs and those of corresponding ORs were inconsistent. For example, lower mean levels of $PM_{2.5}$ and PM_{10} were observed in the second year after birth than the first year, while the ORs in the second year were higher. The findings indicated the increased ORs from 1st year to 2nd and 3rd years were not caused by the changes of the concentrations of PMs.

Our study has several strengths. Apart from $PM_{2.5}$ and PM_{10}, two widely investigated air pollutants, the effects of smaller particles, PM_1, were also evaluated. Individual exposures to three air pollutants were estimated using satellite remote sensing and novel statistical models, which had advantages in predictive accuracy and resolution than traditionally used land use regression (LUR) model without satellite data (Nordio et al., 2013). Apart from prenatal factors, a range of social and demographic risk factors of ASD (e.g., income and educational level of parents) were also considered in our study (Bhasin and Schendel, 2007; Bilder et al., 2009).

Our study also has several limitations. Previous studies have reported some perinatal risk factors for autism such as, breech presentation and low Apgar scores (Guinchat et al., 2012; Hultman et al., 2002). However, it is difficult to isolate the observed effect of post-natal air pollution exposure on ASD from that due to prenatal exposure in this study, as we had no access to participants' prenatal information (e.g., accurate gestational weeks) and family mobility information during pregnancy. Currently, the biological mechanism for the PM-ASD association is not fully understood. For example, it is not clear which exposure period determines the development of ASD (before, during or after pregnancy) and how long it has effects. Given the perinatal information, the overall effects of air pollution on ASD can be better known by considering both the prenatal and postnatal exposures. We did not know the exact onset date of ASD of each case, as in most cases, ASD cases could not get reliable diagnosis until their mid-childhood, especially for children under 3 years old (Baird et al., 2003). This may affect the cause-effect relationship between exposure to air pollution and ASD, as some children may have got ASD during the exposure period. With the actual onset data of disease, cases' exposure can be estimated more accurately, which can contribute to the reliability and robustness of results. However, the effects of this issue may be limited. Modest variations in concentrations of PMs were present in this study, indicating the difference in exposure levels between cases and controls might also exist even with more accurate exposure assessment. Even children's exposures to air pollutants were assessed during 3 years after birth, some of them might already show symptoms of ASD during the exposure period (Johnson and Myers, 2007). We controlled trauma history and parental relationships in the analysis, but these conditions might occur after the ASD symptoms appeared. However, this may not substantially change the results, as the fraction of children with these conditions is small. The methods and models used to predict ground-level PM with satellite remote sensing are advancing rapidly (Ma et al., 2016). The satellite-based prediction is based on the relationships between satellite data and ground measurements of pollutants. In China,

the ground measurements at the country-level are only available after 2013 and ground monitoring stations of PM_1 are limited. Given more historical ground monitoring data and spatial coverage of PM_1 measurements, our satellite-based predictions can be greatly improved in accuracy and time span in the future. We had no access to the mobility information of participants during the study period, but it may not change the results, as the activity radius is about 10 km for most populations in China (Kang et al., 2010; Wu et al., 2014).

In summary, our study provided evidence for the adverse effects of PM on ASD. Despite some studies on air pollution and ASD conducted in western countries (Becerra et al., 2013; Raz et al., 2015), evidence is still limited in low and middle-income countries and in heavily polluted regions, like China. More studies should be focused on the associations between air pollution and children's mental health in the future, as disease like ASD is unlikely to get remission from adolescence onwards and may cause substantial burden across children's lifespan (Baxter et al., 2015). Although many studies have examined the health effects of $PM_{2.5}$ and PM_{10}, knowledge about health effects of smaller particles are very scarce (Kan, 2017). Currently, no standard or policy is available for PM_1 air pollution. Further studies on health effects and toxicology of PM_1 can provide valuable information for policy makers to develop standards for the control of PM_1 air pollution in the future.

5. Conclusions

We found that exposures to PM_1, $PM_{2.5}$ and PM_{10} during the first three years of life significantly increased the risk of ASD. Further studies are warranted to explore the associations between air pollution and mental health, especially in low and middle-income countries. In addition to $PM_{2.5}$ and PM_{10}, the health effects of smaller particles should be given more attention, as they are potentially more harmful.

Competing financial interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.10.026.

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