

Maternal Secondhand Smoke Exposure Enhances Macrosomia Risk among Pregnant Women Exposed to PM_{2.5}: A New Interaction of Two Air Pollutants in A Nationwide Cohort

yunyun Luo

PUMCH: Peking Union Medical College Hospital

yuelun zhang

PUMCH: Peking Union Medical College Hospital

hui pan (✉ panhui20111111@163.com)

PUMCH: Peking Union Medical College Hospital <https://orcid.org/0000-0002-0425-1689>

shi chen

PUMCH: Peking Union Medical College Hospital

Research

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Abstract

BACKGROUND Previous studies have been controversial and inconsistent about fine particulate matter (PM_{2.5}) and secondhand smoking (SHS) air pollutants on neonatal birthweight outcomes and there were no published studies assessing the potential interactive effects between PM_{2.5} and SHS on birthweight outcomes.

PURPOSE To investigate interaction between gestational PM_{2.5} and SHS air pollution exposure on the risk of macrosomia among pregnant women.

METHODS Research data were derived from National Free Preconception Health Examination Project (NFPHEP). Data cleaning process was conducted following strict screening standards to ensure eligibility of participants in our study. Different interaction models about air pollution on birthweight outcomes were established, according to different confounding factors adjustment and different pregnancy stages. SHS subgroups analysis were conducted to further confirm the results of interaction models.

RESULTS Totally, 197877 participants were included in our study. In full-adjusted interaction model, maternal exposure to PM_{2.5} was associated with an increased risk of macrosomia in whole ($p < 0.001$), the first ($p < 0.001$), second ($p < 0.001$) and third ($p < 0.001$) trimester of pregnancy. However, there was a trend for gestational exposure to SHS with risk of low birthweight, but not statistically significant (occasional SHS exposure ($p = 0.099$); frequent SHS exposure ($p = 0.272$)). Interaction effect was statistically significant between maternal exposure to PM_{2.5} and SHS on the risk of macrosomia in the whole pregnancy (all interaction $p < 0.050$) and the first trimester pregnancy (all interaction $p < 0.050$), not in the second (all interaction $p > 0.050$) or third trimester (all interaction $p > 0.050$) of pregnancy. The higher frequency of SHS exposure prompts stronger interaction between the two air pollutants in the whole and the first trimester pregnancy.

CONCLUSIONS In the whole pregnancy and the first trimester pregnancy, maternal exposure to SHS during pregnancy enhances the risk of macrosomia among pregnant women exposed to PM_{2.5} air pollutant, and the interaction became stronger with more frequent exposure to SHS.

Introduction

Birth weight is a key indicator in new-born and infant survival and associated with health outcomes across the whole life course, including cardio-metabolic and mental health, some cancers and mortality^[1, 2]. A fetus larger than 4000g is considered as macrosomia, regardless of gestational age^[3]. Macrosomia is associated with increased risk of maternal and fetal complications such as birth canal trauma, shoulder dystocia, and perinatal asphyxia^[4]. Compared with normal infants, macrosomia newborns are at more risk for long-term complications, such as obesity and insulin resistance^[5]. It was well established that both genetics and environmental risks play indispensable roles in pregnancy outcomes like birth weight^[6, 7]. Genetics risks include parental hereditary material, epigenetic variation and maternal placenta

factors^[8, 9], while environmental risks include gestational air pollutants, maternal addiction to smoking or alcohol, and maternal nutritional condition^[10, 11]. It is more likely to control and intervene environmental risks to improve adverse pregnancy outcomes comparing with the genetics risks. Among environmental risks, fine particulate matter (PM2.5) is one of the most common outdoor air pollutants caused by fossil fuel burning and vehicle emissions, while secondhand smoking (SHS) is the main source of indoor air pollution produced by smokers. Both air pollutants are caused by human activities and can be changed and avoided by taking some measures. Pregnant women exposed to PM2.5 during pregnancy can lead to adverse pregnancy outcomes such as fetal congenital malformation, premature delivery, abnormal birth weight of the fetus, and in severe cases, neonatal death^[12, 13]. Maternal SHS exposure at work and/or at home during pregnancy increased the risk of fetal stillbirth, neonatal death, and perinatal death^[14].

Previous studies have established strongly epidemiologic linkage between prenatal exposure to PM2.5 or SHS and fetal birthweight outcomes. Concerning PM2.5, majority of studies reported that the increased risk of low birth weight (LBW) was associated with maternal exposure to PM2.5^[15]. Links between gestational PM2.5 exposure and small for gestational age (SGA) had been observed in some studies^[10]. A nationwide cohort study suggested that gestational exposure to PM2.5 during pregnancy was significantly associated with an increased risk of macrosomia^[16]. In terms of SHS, evidence on association of neonatal birthweight and cigarette smoke exposure in mothers was accumulated with growing number of studies^[7, 17, 18]. The LBW prevalence was higher among newborns whose mother were prenatally exposed to SHS comparing with newborns whose mother were not exposed^[7]. Link between maternal passive smoking and increased risk of delivering SGA also exists^[18]. All in all, findings of above studies about PM2.5 and SHS air pollutants on neonatal birthweight outcomes have been controversial and inconsistent.

There are some research gaps in areas of association between environment pollutants and infant's birth weight. Firstly, whether the PM2.5 pollutants and SHS were associated with increase or decrease of birth weight was unclear. Secondly, most related studies are confined to certain city or province. Research based on nationwide cohort is limited and scarce. Thirdly, previous studies all evaluated the effects of PM2.5 or SHS air pollutants on birthweight outcomes separately, or considered SHS as possible confounding factor in studies; no published studies have assessed the potential interaction between PM2.5 and SHS and the interactive effects on birthweight outcomes.

In our study, we aimed to investigate the interaction between gestational PM2.5 and SHS air pollution exposure on the risk of macrosomia among pregnant women, and examine the modifying effect of SHS exposure on the association of PM2.5 air pollution and birthweight outcomes during pregnancy. We conducted the data cleaning process of following strict screening standards to ensure the inclusion eligibility of all the enrolled women. We established different interaction models about air pollution on birthweight outcomes, according to different confounding factors adjustment and different pregnancy stages. SHS subgroups analysis were conducted to further confirm the results of interaction models. Our study expended the region of investigation, achieving nationwide evidence including 220 countries from

31 provinces or municipalities in China. This study was the first nationwide, population-based cohort study to identify the interactions between gestational PM_{2.5} and SHS exposure among pregnant women on birthweight outcomes.

Methods

Study Design and Participants

Our research data were derived from the National Free Preconception Health Examination Project (NFPHEP), which lasted 3 years from 1 January 2010 to 31 December 2012. This project was launched by National Health and Family Planning Commission and the Ministry of Finance of the People's Republic of China in 2010. The aim of NFPHEP was to provide free preconception health examinations in rural areas to married couples that planned a pregnancy within the next 6 months. Well-trained local community health workers and obstetricians provided free preconception counselling, medical examinations and managements during pregnancy. In all, at least 240,000 Chinese women in 220 counties from 31 provinces or municipalities of China were enrolled in this project. The study was approved by the institutional review board of the National Research Institute for Family Planning, Beijing, China. All participants provided written informed consent. The detailed study design and implementation of NFPHEP have been described elsewhere^[16, 19, 20].

Referred variables

In this project, information of both enrolled pregnant women and neonates was collected by face-to-face investigation and examination conducted by trained and qualified staff. In total, 371 items in 19 aspects including social demographic characteristics, family history, lifestyle factors, history of diseases, physical examinations, laboratory tests and diagnostic imaging were obtained. All data were uploaded to a nationwide electronic data capture system and underwent quality control by the National Quality Inspection Center for Family Planning Techniques.

The variables analyzed in our study included PM_{2.5} concentration, age at delivery, neonate's birthweight, neonate's sex, educational level, smoking during pregnancy, alcohol intake during pregnancy, prolonged pregnancy, multiparity, pre-pregnancy BMI, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, season of delivery.

Outcome and exposure assessment

As recommended by the World Health Organization, macrosomia was defined as birth weight greater than or equal to 4000 g^[21]. We defined NBW as birth weight between 2500 and 4000 g^[21]. In this study, PM_{2.5} exposure concentration of each country was obtained using a hindcast model specific for historical PM_{2.5} estimation from satellite-retrieved aerosol optical depth. It was an ensemble machine learning model comprised of several machine learning models including random forest, generalized additive model, and extreme gradient boosting. Specific parameter settings and model building have been

reported in detail elsewhere^[16, 22]. Daily county-specific PM2.5 concentration of each included pregnant women was used to calculate monthly PM2.5 concentration to evaluate PM2.5 exposure condition during the pregnancy in our study. The average monthly PM2.5 concentration in 1 to 3 months' gestation, 4 to 6 months' gestation, and 7 months to delivery were regarded as the first, second, and third trimester of pregnancy, respectively. Each woman's address information at the county level has been registered. Secondhand smoke (SHS) is passive inhalation of cigarette smoke produced by smokers' active smoking, also commonly known as "passive smoking" or "forced smoking". Pregnant women in our study may be exposed to different degree of SHS in the workplace or at home. They were divided into three groups according to exposed levels. Those who never touched with smokers or secondhand smokers were classified into "none exposure SHS" subgroup. Those who occasionally visit or work with smokers were classified into "occasional exposure SHS" subgroup. Those who lived with at least one regular smoker were classified into "frequent exposure SHS" subgroup.

The conditions of SHS exposure were collected through the questionnaires filled out by pregnant women.

Statistical Analysis

All the enrolled pregnant women in NFPHEP needed to be screened for the eligibility of inclusion into our study. The definition of loss to follow-up was that participants got preconception examination but had not received prenatal or postnatal examination and questionnaires yet by 1 month after expected date of confinement. To avoid the bias induced by moving during pregnancy, women who had a different registered residence and birthplace were excluded. The pregnancy women who had missing data of PM2.5 concentration, birthweight, SHS conditions were excluded in analysis. Extreme or abnormal observations in other variables were replaced with missing data or censored data, which was not excluded in analysis.

The establishment of interaction models was based on binary logistic regression, including main effects item, interaction effects item and other confounding factors adjustment. The interaction model varied among different pregnancy stages. The confounding factors adjustment strategies of the whole pregnancy followed layer upon layer progressive principles. Four models were constructed on the basis of previous model one by one. Model 1 included merely three independent variables: PM2.5 concentration, different exposure levels of SHS, the interaction between PM2.5 and SHS. On the basis of model 1, maternal age at delivery, and pre-pregnancy body mass index (BMI) were added in the model 2, and then neonate's sex (male, female), prolonged pregnancy ≥ 42 weeks (yes, no), and multiparity (yes, no) were added in the model 3. On the basis of model 3, preconception diabetes (yes, no), preconception hypertension (yes, no), family history of diabetes (yes, no), the highest maternal educational level (junior high school, senior high school, college), season of delivery (spring: March to May, summer: June to August, autumn: September to December, winter: November to February), and alcohol consumption status (still, quit, never) were added in the fully adjusted model 4. The confounding factors adjustment strategies of the first, second, and third trimester of pregnancy followed full-adjusted principle and three

trimesters all adopted the model 4 above to evaluate the trimester-specific interaction effect. Odds ratios (ORs) and its 95% confidence intervals (CI) were reported.

To further confirm the results of interactive model, we conducted subgroup analyses stratified by SHS exposure (None exposure, Occasional exposure, Frequent exposure). In each exposure level of SHS, binary logistic regression was established to evaluate the association between trimester-specific PM2.5 and fetal macrosomia. Odds ratios (ORs) and its 95% confidence intervals (CI) were reported.

The data cleaning was conducted using Stata 16. All the interaction models and SHS subgroup analyses were performed using R 4.0.3. A two-sided P value less than 0.05 was considered statistically significant. This study used the secondary data source; therefore, the statistical power using the available number of participants was estimated.

Results

In this study, we initially obtained 248501 pregnancy women between January 1,2010 to December 31, 2012 from the NFPHEP. After 6914 mismatch of birthplace and follow-up place or missing removed, 241587 participants involved preliminarily. Participants lost to follow-up (5036), unreported birthweight (26275), unreported gestational PM2.5 concentration (1121), unreported SHS exposure (7471) and active smoking (1434) were excluded. Pregnancy women with adverse pregnancy outcomes including birth defects (177), spontaneous abortion (121), medical abortion (24), induced labour (136), still births (332), LBW (484) were also excluded. after 1099 non-singleton births pregnancies removed. The selection process, including reasons for excluding pregnancy women, is summarized in a flow diagram (Figure A.1). Finally, 197877 participants were included in the current study

Table 1 shows the baseline characteristic of women and neonates included. Among all newborns (n = 197877), macrosomia (n = 15348) account for 7.76% and the last were non- macrosomia (n = 182529). Male neonates (n = 9191) are more than female neonates (n = 6140) among macrosomia group. The median birth weight of the whole study newborns is 3300(3000, 3600). Other characteristics were also clearly shown in Table 1.

Table 2 summaries the median concentration of PM2.5 during pregnancy according to different pregnancy stages. The whole, first, second, third semester pregnancy has 78.97, 68.96, 70.03, and 81.71 $\mu\text{g}/\text{m}^3$ PM2.5 exposure respectively in the macrosomia group, and 76.93, 67.50, 67.50, and 79.04 $\mu\text{g}/\text{m}^3$ PM2.5 respectively in the overall group.

Table 3 shows the interaction between PM2.5 exposure in whole pregnancy and SHS exposure on risk of macrosomia. Among the four models, the latter model in turn adds some confounding factors on the basis of the previous model. In each interactive model, maternal exposure to PM2.5 during pregnancy was associated with an increased risk of macrosomia in whole pregnancy separately ($p < 0.001$; $p < 0.001$; $p < 0.001$; $p < 0.001$). However, there was no significant association between different frequency of SHS exposure and risk of macrosomia, not only occasional SHS exposure ($p = 0.246$; $p = 0.124$; $p = 0.116$; $p =$

0.099), but also frequent SHS exposure ($p = 0.374$; $p = 0.289$; $p = 0.289$; $p = 0.272$). In contrast, a trend was observed for gestational exposure to SHS with risk of low birth weight, but not statistically significant. From model 1 to 4, the odds ratio of occasional SHS exposure (OR = 0.916; OR = 0.889; OR = 0.889; OR = 0.881) and frequent SHS exposure (OR = 0.838; OR = 0.809; OR = 0.809; OR = 0.812) were < 1 . Interaction effect was statistically significant between maternal exposure to PM2.5 and SHS on the risk of macrosomia (interaction $p < 0.05$). In four different confounding factors-adjusted models, different frequency of SHS exposure all significantly enhances risk of macrosomia among pregnant women exposed to PM2.5 air pollutant (interaction $p < 0.05$). From model 1 to 4, interaction effect between occasional SHS exposure and PM2.5 were significant (interaction $p = 0.021$; $p = 0.010$; $p = 0.010$; $p = 0.010$), which the same as interaction effect between frequent SHS exposure and PM2.5 (interaction $p = 0.050$; $p = 0.046$; $p = 0.051$; $p = 0.047$). The higher exposure times and intensities of SHS prompts the stronger interaction between the two air pollutants. From model 1 to 4, the odds ratio of PM2.5 & Frequent SHS exposure was larger than PM2.5 & Occasional SHS exposure (OR = 1.004 $>$ OR = 1.002; OR = 1.005 $>$ OR = 1.002; OR = 1.004 $>$ OR = 1.002; OR = 1.005 $>$ OR = 1.002). The odds ratio of all confounding factors in model 4 were listed in **TABLE A.1**.

Table 4 shows the interaction between PM2.5 exposure in first trimester, second trimester and third trimester of pregnancy and SHS exposure on risk of macrosomia. Each interactive model was based on full confounding factors-adjusted model. In the first trimester, the interaction effect was statistically significant between maternal exposure to PM2.5 and occasional SHS exposure on the risk of macrosomia (interaction $p < 0.001$). Occasionally exposed to SHS significantly enhances risk of macrosomia among pregnant women exposed to PM2.5 air pollutant (interaction $p < 0.001$). Frequently exposed to SHS was not associated with the risk of macrosomia among pregnant women exposed to PM2.5 air pollutant (interaction $p = 0.100$). In the second or third trimester, there is no interactive effect between maternal PM2.5 exposure and occasional exposed to SHS (interaction $p = 0.081$; $p = 0.592$). There is no interactive effect between maternal PM2.5 exposure and frequent exposed to SHS during second or third trimester of pregnancy, either (interaction $p = 0.302$; $p = 0.067$).

Table 5 represents the association between PM2.5 concentration in different stages of pregnancy and the risk of macrosomia in different SHS Subgroups. The results of whole pregnancy are consistent with results of first trimester. The higher exposure concentration of PM2.5 during the whole pregnancy or the first trimester among pregnant women was associated with the higher risk of macrosomia (OR = 1.004, $p < 0.001$; OR = 1.003, $p < 0.001$). Different frequency of SHS exposure all significantly increases risk of macrosomia among pregnant women exposed to PM2.5 air pollutant, not only exposed to SHS occasionally (interaction $p < 0.001$; $p < 0.001$), but also exposed to SHS frequently (interaction $p < 0.001$; $p < 0.001$). More frequently exposed to SHS among pregnant women induces stronger interactive effect between PM2.5 and SHS air pollutants during the whole pregnancy (Frequent exposure OR = 1.007 $>$ Occasional exposure OR = 1.006) and the first trimester (Frequent exposure OR = 1.008 $>$ Occasional exposure OR = 1.006). In the second and the third trimester, maternal PM2.5 exposure is associated with an increased risk of macrosomia (OR = 1.003, $p < 0.001$; OR = 1.002, $p < 0.001$). But there is no interaction between maternal PM2.5 exposure and SHS exposure in the second (OR = 1.003, $p < 0.001$; OR = 1.005, p

< 0.001; OR = 1.004, p = 0.069) and the third trimester (OR = 1.002, p < 0.001; OR = 1.005, p < 0.001; OR = 1.005, p = 0.007).

Discussion

In full-adjusted interaction model, we found maternal exposure to PM_{2.5} was associated with an increased risk of macrosomia in whole pregnancy (p < 0.001), the first (p < 0.001), second (p < 0.001) and third (p < 0.001) trimester of pregnancy. However, there was a trend for gestational exposure to SHS with risk of low birth weight, but not statistically significant (occasional SHS exposure (p = 0.099); frequent SHS exposure (p = 0.272)). Interaction effect was statistically significant between maternal exposure to PM_{2.5} and SHS on the risk of macrosomia in the whole pregnancy (all interaction p < 0.050) and the first trimester pregnancy (all interaction p < 0.050), not in the second trimester (all interaction p > 0.050) and third trimester (all interaction p > 0.050) of pregnancy. The higher frequency of SHS exposure prompts the stronger interaction between the two air pollutants in the whole pregnancy and the first trimester pregnancy. In conclusion, in the whole pregnancy and the first trimester pregnancy, maternal exposure to SHS during pregnancy enhances the risk of macrosomia among pregnant women exposed to PM_{2.5} air pollutant, and the interaction became stronger with the more frequent exposure to SHS.

There is a rigorous methodology in our study. First, the process of data cleaning was conducted following strict screening standards. All the enrolled pregnant women in NFPHEP needed to be screened for the eligibility of inclusion into our study. Second, the confounding factors were adjusted gradually in different models and avoid making bias to the outcomes. Third, the subgroup analyses stratified by SHS exposure were conducted to further confirm the results of interactive model.

There are several innovations in our research. First, our study was conducted among a new study population, that is, the national pregnant Chinese women. Previous studies on the adverse effect of air pollution on birth outcomes were mostly carried out in developed countries or regions^[23, 24]. The differences between Chinese and foreigner population reflected in several aspects, such as the higher exposure condition of maternal SHS^[25, 26], higher PM_{2.5} pollution levels^[27, 28] and more vulnerable metabolism characteristics of Chinese population comparing with foreigners^[29, 30]. Hence, our study could provide new evidence on prognosis of air pollutions-related diseases among Chinese population, which represent 1/3 of the world's population. Second, our study establishes a new interaction model between two human-caused air pollutants. Previous studies focused on the interaction between genetic inheritance and environmental pollutants on birth outcomes^[31, 32]. No study pays attention to the interaction between two air pollutants caused by human activities during different stages of pregnancy, and the two air pollutants can be changed and avoided by taking some measures. Third, our study identifies a new risk that can intensity the association between maternal PM_{2.5} air pollutant exposure and macrosomia newborns. We found maternal SHS exposure enhances the risk of macrosomia associated with PM_{2.5} exposure.

Our study found maternal exposure to PM_{2.5} during pregnancy was associated with an increased risk of macrosomia in whole pregnancy and different stages of pregnancy. The finding was consistent with previous study on association between PM_{2.5} exposure and birth weight^[16]. In CHEN et al's study^[16], significant associations were found between increased risk of macrosomia and every 10 µg/m³ increase of PM_{2.5} concentration over the first, second, and third trimesters in a nationwide prospective cohort study in China. Furthermore, our study also found a trend of low birth weight for gestational exposure to SHS, although it was not statistically significant. The trend in our study was consistent with most previous studies on association of neonatal birthweight and cigarette smoke exposure in mothers^[7, 17, 18]. In a cross-sectional study from Shanghai, WANG et al^[7] found that the LBW prevalence was higher among newborns whose mother were prenatally exposed to SHS comparing with newborns whose mother were not exposed. KOBAYASHI et al's study^[18] also observed the link between maternal passive smoking and increased risk of delivering SGA in a prospective birth cohort from the Hokkaido.

Our study suggested there are interaction between maternal exposure to SHS and PM_{2.5} air pollutants on the risk of macrosomia in the whole pregnancy and the first trimester pregnancy. The higher frequency of SHS exposure prompts the stronger interaction between the two air pollutants in the whole pregnancy and the first trimester pregnancy. No studies before have concentrated on the interaction effect of two air pollutants on adverse pregnancy outcomes such as birth weight. The interaction between air pollutants and other factors on birth weight outcome have been reported in previous studies. Huang et al.^[33] examine the interaction effects of prenatal exposed to environmental tobacco smoke (ETS) and genotypes of cytochrome P4501A1 (CYP1A1), glutathione S-transferases (GSTs) on the risk of full-term low birth weight (FT-LBW). The study^[33] revealed that gene polymorphisms of CYP1A1 and GSTs played modified roles in associations between prenatal ETS exposure and FT-LBW. However, it is harder to take measures to change genetic endowments, compared with controlling man-made pollutant factors like PM_{2.5} and SHS exposure in our study. Wang et al. and colleagues^[34] also assessed the interaction of air pollutants and meteorological factors on birth weight in Shenzhen, China. According to Wang's research^[34], an interactive effect of air temperature and humidity on the relationship between PM₁₀ exposure and SGA among newborns existed. Other studies also reported interaction between air pollutants and life-related risk factors of mothers during pregnancy on fetal birth weight, such as maternal pre-pregnancy overweight^[35], maternal employment^[36], and maternal illicit drug use^[37]. But in all, there have been no studies before assessing the interaction effect of two air pollutants on birth weight outcomes.

The detailed mechanism of interaction between maternal exposure to SHS and PM_{2.5} air pollutants on the risk of macrosomia during pregnancy remains unclear. A few possible explanations or hypothesis are as follows. Firstly, SHS is the main source of indoor PM_{2.5} pollution that could be inhaled into lung and blood circulation^[38, 39]. When SHS exposure from surrounding smokers and PM_{2.5} exposure from atmosphere existed simultaneously, the concentration of PM_{2.5} changed and certain effect like synthesis may happened. Hence it is possible that there was interaction between maternal exposure to SHS and PM_{2.5}. Secondly, studies on association of PM_{2.5} air pollutant and infant's birth weight outcome

suggested changes of oxidative stress^[40], immune response^[41] and epigenetic regulation^[42] may influence birth weight. Furthermore, studies on association of maternal tobacco smoke exposure and fetal birth weight suggested that placental toxicity^[43] and epigenetic modifications such as DNA methylation^[44] could be potential mediators affecting fetal birth weight outcomes. So epigenetic modifications could be an explanation for the interaction between maternal exposure to SHS and PM2.5 air pollutants on the risk of macrosomia. Maybe the two air pollutants have some common gene methylation or overlapped molecular pathway of macrosomia leading to the interaction. It seems controversial that maternal SHS exposure alone led to a trend of low birth weight, however, in the interaction effect, SHS could enhance the risk of macrosomia among pregnant women exposed to PM2.5 air pollutant in our study. The explanation may be that the gene or signal pathway related with association between SHS and macrosomia could only be activated by gene or signal pathway related with PM2.5. SHS exposure alone could not lead to macrosomia, because macrosomia-related genes were not activated by PM2.5. Our study suggested only in the whole pregnancy and the first trimester, the interaction between maternal exposure to SHS and PM2.5 air pollutants on the risk of macrosomia existed. The result indicates that the exposure to PM2.5 in the first trimester might have the biggest effect on birth weight. It might be because that the exposure to air pollution in the first trimester could lead to placental adaptation through epigenetic modification^[45].

Our study has some strengths and several potential limitations. The strengths include emphasis on the harm of SHS to pregnant women, especially in high-exposed PM2.5 regions. Another strength is to point out the study direction that future studies should focus on the epigenetic aspects when exploring the mechanism of birth weight changes associated with the environmental pollutants such as PM2.5 or SHS exposure. The study had also some limitations. Majority of pregnant women in the NFPHEP were from rural areas in China, and thus, the conclusions made in this study are most pertinent to this region. Since the survey of SHS condition in our study was conducted through the questionnaire completed by the pregnant women, the collected information could be inevitably influenced by subjective ideas. Another limitation of our study was the potential recall bias due to the long follow-up interval.

Generally, our study highlights the impact of environmental air pollutants on adverse pregnancy outcomes like birth weight and we should emphasize on controllable human activities-caused environmental pollutants like PM2.5 and SHS, which could be reduced or removed by taking some measures in future. Our results strengthened evidence that maternal exposure to PM2.5 during pregnancy was associated with an increased risk of macrosomia in China and meanwhile, firstly suggested that SHS may enhance the risk of macrosomia associated with PM2.5. So pregnant women should avoid exposure to SHS during pregnancy, especially those who lived in areas with serious PM2.5 pollution and who were in the first trimester of pregnancy. These findings may help to identify high-risk pregnant women for giving birth to macrosomia, providing an opportunity for targeted preventive interventions to protect vulnerable population as early as possible. Strengthening air pollution control will have a beneficial impact on avoiding adverse birth outcomes, improving the quality of national population and alleviating national financial burden. Furthermore, the results of our study also suggested that the

detailed mechanism of pregnancy outcome should focus more on epigenetic aspects of embryonic development in future.

Conclusion

In the whole pregnancy and the first trimester pregnancy, maternal exposure to SHS during pregnancy enhances the risk of macrosomia among pregnant women exposed to PM2.5 air pollutant, and the interaction became stronger with the more frequent exposure to SHS.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of the National Research Institute for Family Planning, Beijing, China.

Consent for publication

All participants provided written informed consent.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

LYY has drafted the work and completed the manuscript.

ZYL has made substantial contributions to the acquisition, analysis, or interpretation of data for the work;

PH has provided editing and writing assistance for important intellectual content;

CS has made substantial contributions to the conception or design of the work;

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References

- [1] O'DONNELL K J, MEANEY M J. Fetal Origins of Mental Health: The Developmental Origins of Health and Disease Hypothesis [J]. *The American journal of psychiatry*, 2017, 174(4): 319-28.
- [2] RISNES K R, VATTEN L J, BAKER J L, et al. Birthweight and mortality in adulthood: a systematic review and meta-analysis [J]. *International journal of epidemiology*, 2011, 40(3): 647-61.
- [3] ARAUJO JÚNIOR E, PEIXOTO A B, ZAMARIAN A C, et al. Macrosomia [J]. *Best practice & research Clinical obstetrics & gynaecology*, 2017, 38(83-96).
- [4] BETA J, KHAN N, KHALIL A, et al. Maternal and neonatal complications of fetal macrosomia: systematic review and meta-analysis [J]. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*, 2019, 54(3): 308-18.
- [5] KC K, SHAKYA S, ZHANG H. Gestational diabetes mellitus and macrosomia: a literature review [J]. *Annals of nutrition & metabolism*, 2015, 66 Suppl 2(14-20).
- [6] KÜPERS L K, MONNEREAU C, SHARP G C, et al. Meta-analysis of epigenome-wide association studies in neonates reveals widespread differential DNA methylation associated with birthweight [J]. *Nature communications*, 2019, 10(1): 1893.
- [7] WANG R, SUN T, YANG Q, et al. Low birthweight of children is positively associated with mother's prenatal tobacco smoke exposure in Shanghai: a cross-sectional study [J]. *BMC pregnancy and childbirth*, 2020, 20(1): 603.
- [8] BEAUMONT R N, KOTECHE S J, WOOD A R, et al. Common maternal and fetal genetic variants show expected polygenic effects on risk of small- or large-for-gestational-age (SGA or LGA), except in the smallest 3% of babies [J]. *PLoS genetics*, 2020, 16(12): e1009191.
- [9] CREETH H D J, JOHN R M. The placental programming hypothesis: Placental endocrine insufficiency and the co-occurrence of low birth weight and maternal mood disorders [J]. *Placenta*, 2020, 98(52-9).
- [10] YUAN L, ZHANG Y, GAO Y, et al. Maternal fine particulate matter (PM_{2.5}) exposure and adverse birth outcomes: an updated systematic review based on cohort studies [J]. *Environmental science and pollution research international*, 2019, 26(14): 13963-83.
- [11] GRANGÉ G, BERLIN I, BRETTELLE F, et al. Smoking and smoking cessation in pregnancy. Synthesis of a systematic review [J]. *Journal of gynecology obstetrics and human reproduction*, 2020, 49(8): 101847.
- [12] WOJTYLA C, ZIELINSKA K, WOJTYLA-BUCIORA P, et al. Prenatal Fine Particulate Matter (PM_{2.5}) Exposure and Pregnancy Outcomes-Analysis of Term Pregnancies in Poland [J]. *International journal of environmental research and public health*, 2020, 17(16):

- [13] TAPIA V L, VASQUEZ B V, VU B, et al. Association between maternal exposure to particulate matter (PM(2.5)) and adverse pregnancy outcomes in Lima, Peru [J]. *Journal of exposure science & environmental epidemiology*, 2020, 30(4): 689-97.
- [14] PINELES B L, HSU S, PARK E, et al. Systematic Review and Meta-Analyses of Perinatal Death and Maternal Exposure to Tobacco Smoke During Pregnancy [J]. *American journal of epidemiology*, 2016, 184(2): 87-97.
- [15] LIU Y, XU J, CHEN D, et al. The association between air pollution and preterm birth and low birth weight in Guangdong, China [J]. *BMC public health*, 2019, 19(1): 3.
- [16] CHEN S, WANG S, LI T, et al. Effect of PM2.5 on macrosomia in China: A nationwide prospective cohort study [J]. *Pediatric obesity*, 2020, 15(2): e12584.
- [17] EDI M, CHIN Y S, WOON F C, et al. Inadequate Gestational Weight Gain and Exposure to Second-Hand Smoke during Pregnancy Increase the Risk of Low Birth Weight: A Cross-Sectional Study among Full-Term Infants [J]. *International journal of environmental research and public health*, 2021, 18(3):
- [18] KOBAYASHI S, SATA F, HANAOKA T, et al. Association between maternal passive smoking and increased risk of delivering small-for-gestational-age infants at full-term using plasma cotinine levels from The Hokkaido Study: a prospective birth cohort [J]. *BMJ open*, 2019, 9(2): e023200.
- [19] PAN Y, ZHANG S, WANG Q, et al. Investigating the association between prepregnancy body mass index and adverse pregnancy outcomes: a large cohort study of 536 098 Chinese pregnant women in rural China [J]. *BMJ open*, 2016, 6(6): e011227.
- [20] WANG Y Y, LI Q, GUO Y, et al. Association of Long-term Exposure to Airborne Particulate Matter of 1 μm or Less With Preterm Birth in China [J]. *JAMA pediatrics*, 2018, 172(3): e174872.
- [21] YE J, TORLONI M R, OTA E, et al. Searching for the definition of macrosomia through an outcome-based approach in low- and middle-income countries: a secondary analysis of the WHO Global Survey in Africa, Asia and Latin America [J]. *BMC pregnancy and childbirth*, 2015, 15(324).
- [22] XIAO Q, CHANG H H, GENG G, et al. An Ensemble Machine-Learning Model To Predict Historical PM(2.5) Concentrations in China from Satellite Data [J]. *Environmental science & technology*, 2018, 52(22): 13260-9.
- [23] ADIBELLI D, KIRCA N. The relationship between gestational active and passive smoking and early postpartum complications [J]. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*, 2020, 33(14): 2473-9.
- [24] CARRERAS G, LACHI A, CORTINI B, et al. Burden of disease from exposure to secondhand smoke in children in Europe [J]. *Pediatric research*, 2020,

- [25] BOULET S L, ALEXANDER G R, SALIHU H M, et al. Macrosomic births in the united states: determinants, outcomes, and proposed grades of risk [J]. *American journal of obstetrics and gynecology*, 2003, 188(5): 1372-8.
- [26] Fetal macrosomia. ACOG Technical Bulletin Number 159–September 1991 [J]. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, 1992, 39(4): 341-5.
- [27] LI X, HUANG S, JIAO A, et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis [J]. *Environmental pollution (Barking, Essex : 1987)*, 2017, 227(596-605).
- [28] ZHAO N, QIU J, MA S, et al. Effects of prenatal exposure to ambient air pollutant PM10 on ultrasound-measured fetal growth [J]. *International journal of epidemiology*, 2018, 47(4): 1072-81.
- [29] LU J, WANG L, LI M, et al. Metabolic Syndrome Among Adults in China: The 2010 China Noncommunicable Disease Surveillance [J]. *The Journal of clinical endocrinology and metabolism*, 2017, 102(2): 507-15.
- [30] XU Y, WANG L, HE J, et al. Prevalence and control of diabetes in Chinese adults [J]. *Jama*, 2013, 310(9): 948-59.
- [31] HE F, LIN J, YU T, et al. [Interaction research on smoking and microRNA genes SNP related to lung cancer in Fujian Han population] [J]. *Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]*, 2016, 50(2): 168-74.
- [32] HEDSTRÖM A K, BOMFIM I L, BARCELLOS L F, et al. Interaction between passive smoking and two HLA genes with regard to multiple sclerosis risk [J]. *International journal of epidemiology*, 2014, 43(6): 1791-8.
- [33] HUANG L, LUO Y, WEN X, et al. Gene-gene-environment interactions of prenatal exposed to environmental tobacco smoke, CYP1A1 and GSTs polymorphisms on full-term low birth weight: relationship of maternal passive smoking, gene polymorphisms, and FT-LBW [J]. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet*, 2019, 32(13): 2200-8.
- [34] WANG Q, LIANG Q, LI C, et al. Interaction of Air Pollutants and Meteorological Factors on Birth Weight in Shenzhen, China [J]. *Epidemiology (Cambridge, Mass)*, 2019, 30 Suppl 1(S57-s66).
- [35] CHATTRAPIBAN T, SMIT H A, WIJGA A H, et al. The joint effect of maternal smoking during pregnancy and maternal pre-pregnancy overweight on infants' term birth weight [J]. *BMC pregnancy and childbirth*, 2020, 20(1): 132.

- [36] CHOE S A, JANG J, KIM M J, et al. Association between ambient particulate matter concentration and fetal growth restriction stratified by maternal employment [J]. *BMC pregnancy and childbirth*, 2019, 19(1): 246.
- [37] REYNOLDS C M E, EGAN B, DALY N, et al. The interaction between maternal smoking, illicit drug use and alcohol consumption associated with neonatal outcomes [J]. *Journal of public health (Oxford, England)*, 2020, 42(2): 277-84.
- [38] HIRANO T, SHOBAYASHI T, TAKEI T, et al. Exposure Assessment of Environmental Tobacco Aerosol from Heated Tobacco Products: Nicotine and PM Exposures under Two Limited Conditions [J]. *International journal of environmental research and public health*, 2020, 17(22):
- [39] YAMATO H, KATO T, JIANG Y, et al. Secondhand Smoke from a Veranda Spreading to Neighboring Households [J]. *Journal of UOEH*, 2020, 42(4): 335-8.
- [40] VALAVANIDIS A, FIOTAKIS K, BAKEAS E, et al. Electron paramagnetic resonance study of the generation of reactive oxygen species catalysed by transition metals and quinoid redox cycling by inhalable ambient particulate matter [J]. *Redox report : communications in free radical research*, 2005, 10(1): 37-51.
- [41] BEZEMER G F, BAUER S M, OBERDÖRSTER G, et al. Activation of pulmonary dendritic cells and Th2-type inflammatory responses on instillation of engineered, environmental diesel emission source or ambient air pollutant particles in vivo [J]. *Journal of innate immunity*, 2011, 3(2): 150-66.
- [42] JANSSEN B G, GODDERIS L, PIETERS N, et al. Placental DNA hypomethylation in association with particulate air pollution in early life [J]. *Particle and fibre toxicology*, 2013, 10(22).
- [43] ROGERS J M. Smoking and pregnancy: Epigenetics and developmental origins of the metabolic syndrome [J]. *Birth defects research*, 2019, 111(17): 1259-69.
- [44] KHEIRKHAH RAHIMABAD P, ANTHONY T M, JONES A D, et al. Nicotine and Its Downstream Metabolites in Maternal and Cord Sera: Biomarkers of Prenatal Smoking Exposure Associated with Offspring DNA Methylation [J]. *International journal of environmental research and public health*, 2020, 17(24):
- [45] MAGHBOOLI Z, HOSSEIN-NEZHAD A, ADABI E, et al. Air pollution during pregnancy and placental adaptation in the levels of global DNA methylation [J]. *PloS one*, 2018, 13(7): e0199772.

Tables

Table 1
Baseline characteristics of the included pregnant women and neonates

Characteristics	Macrosomia		Overall (n = 197877)
	Yes (n = 15348)	No (n = 182529)	
Birth weight, g	4322.43 ± 469.90	3234.18 ± 428.42	3318.59 ± 520.74
Neonate's sex			
Male	9191 (59.90%)	95332 (52.20%)	104523 (52.80%)
Female	6140 (40.00%)	87101 (47.70%)	93241 (47.10%)
Missing	17 (0.10%)	96 (0.10%)	113 (0.10%)
Age at delivery, y	25.32 ± 3.97	25.23 ± 3.93	25.24 ± 3.94
Pre-pregnancy BMI ^a , kg/m ²	21.30 ± 2.76	21.02 ± 2.60	21.04 ± 2.61
Prolonged pregnancy			
Yes	523 (3.40%)	4103 (2.20%)	4626 (2.30%)
No	14825 (96.60%)	178426 (97.80%)	193251 (97.70%)
Multiparity			
Yes	11894 (77.50%)	37983 (20.80%)	49877 (25.20%)
No	3454 (22.50%)	144546 (79.20%)	148000 (74.80%)
Highest education level			
Junior high school	10753 (70.10%)	128280 (70.30%)	139033 (70.30%)
Senior high school	2892 (18.80%)	34594 (19.00%)	37486 (18.90%)
College	1532 (10.00%)	17368 (9.50%)	18900 (9.60%)
Missing	171 (1.10%)	2287 (1.20%)	2458 (1.20%)
Pre-pregnancy diabetes mellitus			
Yes	3 (0.02%)	18 (0.05%)	21 (0.01%)
No	15345 (99.98%)	178426 (97.75%)	193771 (97.93%)
Missing	0 (0.00%)	4085 (2.20%)	4085 (2.06%)
Pre-pregnancy hypertension			
Yes	8 (0.05%)	93 (0.10%)	101 (0.10%)
No	15340 (99.95%)	182436 (99.90%)	197776 (99.90%)

Characteristics	Macrosomia		Overall (n = 197877)
	Yes (n = 15348)	No (n = 182529)	
Family history of diabetes mellitus			
Yes	100 (0.70%)	1040 (0.60%)	1140 (0.60%)
No	15248 (99.30%)	181489 (99.40%)	196737 (99.40%)
Drinking during pregnancy			
Never	15205 (99.10%)	180573 (98.90%)	195778(98.90%)
Quit	99 (0.60%)	1169 (0.60%)	1268 (0.60%)
Still	35 (0.20%)	720 (0.40%)	755 (0.40%)
Missing	9 (0.10%)	67 (0.10%)	76 (0.10%)
Season of delivery			
Spring	4065 (26.50%)	48959 (26.80%)	53024 (26.80%)
Summer	2421 (15.80%)	28626 (15.70%)	31047 (15.70%)
Autumn	3897 (25.40%)	47184 (25.90%)	51081 (25.80%)
Winter	4965 (32.30%)	57760 (31.60%)	62725 (31.70%)
Secondhand Smoking			
None exposure	12320 (80.30%)	149308 (81.80%)	161628 (81.70%)
Occasional exposure	2683 (17.50%)	29845 (16.40%)	32528 (16.40%)
Frequent exposure	345 (2.20%)	3376 (1.80%)	3721 (1.90%)

^aBMI, body mass index.

Table 2
Mean PM2.5 concentration during pregnancy ($\mu\text{g}/\text{m}^3$)

Stage of Pregnancy	Macrosomia		Overall (n = 197877)
	Yes (n = 15348)	No (n = 182529)	
First trimester	73.35 \pm 29.25	70.81 \pm 29.26	71.01 \pm 29.27
Second trimester	73.82 \pm 29.00	71.67 \pm 29.97	71.83 \pm 29.90
Third trimester	83.88 \pm 32.46	81.23 \pm 33.08	81.43 \pm 33.04
whole pregnancy	77.57 \pm 22.11	75.08 \pm 22.93	75.28 \pm 22.87

Table 3

The interaction between PM2.5 exposure in whole pregnancy and SHS exposure on risk of macrosomia

	Odds Ratio(95%CI)	P value
whole pregnancy		
Model 1 ^a		
PM2.5 exposure	1.004 (1.003, 1.005)	< 0.001
Occasional SHS ^e exposure	0.916 (0.789, 1.062)	0.246
Frequent SHS exposure	0.838 (0.565, 1.228)	0.374
PM2.5 & Occasional SHS exposure ^f	1.002 (1.000, 1.004)	0.021
PM2.5 & Frequent SHS exposure ^g	1.004 (1.000, 1.009)	0.050
Model 2 ^b		
PM2.5 exposure	1.004 (1.003, 1.005)	< 0.001
Occasional SHS exposure	0.889 (0.765, 1.032)	0.124
Frequent SHS exposure	0.809 (0.544, 1.189)	0.289
PM2.5 & Occasional SHS exposure	1.002 (1.000, 1.004)	0.010
PM2.5 & Frequent SHS exposure	1.005 (1.000, 1.009)	0.046
Model 3 ^c		
PM2.5 exposure	1.004 (1.003, 1.004)	< 0.001

^aUnadjusted^bAdjusted for age at delivery, pre-pregnancy BMI^cAdjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, and multiparity^dAdjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, multiparity, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, educational level, drinking during pregnancy, and season of delivery.^eSHS, secondhand smoking.^fThe interaction between mean PM2.5 concentration of whole pregnancy and occasional SHS exposure^gThe interaction between mean PM2.5 concentration of whole pregnancy and frequent SHS exposure

	Odds Ratio(95%CI)	P value
	whole pregnancy	
Occasional SHS exposure	0.889 (0.763, 1.029)	0.116
Frequent SHS exposure	0.809 (0.542, 1.190)	0.289
PM2.5 & Occasional SHS exposure	1.002 (1.001, 1.004)	0.010
PM2.5 & Frequent SHS exposure	1.004 (1.000, 1.009)	0.051
Model 4 ^d		
PM2.5 exposure	1.004 (1.003, 1.005)	< 0.001
Occasional SHS exposure	0.881 (0.757, 1.024)	0.099
Frequent SHS exposure	0.812 (0.537, 1.181)	0.272
PM2.5 & Occasional SHS exposure	1.002 (1.001, 1.004)	0.010
PM2.5 & Frequent SHS exposure	1.005 (1.000, 1.009)	0.047
^a Unadjusted		
^b Adjusted for age at delivery, pre-pregnancy BMI		
^c Adjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, and multiparity		
^d Adjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, multiparity, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, educational level, drinking during pregnancy, and season of delivery.		
^e SHS, secondhand smoking.		
^f The interaction between mean PM2.5 concentration of whole pregnancy and occasional SHS exposure		
^g The interaction between mean PM2.5 concentration of whole pregnancy and frequent SHS exposure		

Table 4

The interaction between PM2.5 exposure in first trimester, second trimester and third trimester of pregnancy and SHS exposure on risk of macrosomia

	Odds Ratio (95%CI)	P value
First trimester ^a		
PM2.5 exposure	1.003 (1.002, 1.004)	< 0.001
Occasional SHS ^e exposure ^b	0.826 (0.734, 0.929)	0.001
Frequent SHS exposure	0.929 (0.683, 1.253)	0.631
PM2.5 & Occasional SHS exposure	1.003 (1.002, 1.005)	0.000
PM2.5 & Frequent SHS exposure	1.003 (0.999, 1.007)	0.100
Second trimester ^a		
PM2.5 exposure	1.003 (1.002, 1.004)	< 0.001
Occasional SHS exposure ^c	0.970 (0.865, 1.087)	0.604
Frequent SHS exposure	1.013 (0.742, 1.373)	0.936
PM2.5 & Occasional SHS exposure	1.001 (0.999, 1.003)	0.081
PM2.5 & Frequent SHS exposure	1.002 (0.998, 1.005)	0.302
Third trimester ^a		
PM2.5 exposure	1.003 (1.002, 1.003)	< 0.001
Occasional SHS exposure ^d	1.036 (0.922, 1.163)	0.551
Frequent SHS exposure	0.905 (0.664, 1.224)	0.524
PM2.5 & Occasional SHS exposure	1.003 (0.999, 1.002)	0.592
PM2.5 & Frequent SHS exposure	1.003 (0.999, 1.006)	0.067

	Odds Ratio (95%CI)	P value
^a Adjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, multiparity, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, educational level, drinking during pregnancy, and season of delivery.		
^b The interaction between mean PM2.5 concentration of first trimester pregnancy and occasional SHS exposure.		
^c The interaction between mean PM2.5 concentration of second trimester pregnancy and occasional SHS exposure.		
^d The interaction between mean PM2.5 concentration of third trimester pregnancy and occasional SHS exposure.		
^e SHS, secondhand smoking.		

Table 5

Association between PM2.5 concentration in different stages of pregnancy and the risk of macrosomia in different SHS Subgroups.

	SHS ^b Subgroup	Odds Ratio(95%CI)	P value
Whole pregnancy ^a	None exposure	1.004 (1.003, 1.005)	< 0.001
	Occasional exposure	1.006 (1.005, 1.008)	< 0.001
	Frequent exposure	1.007 (1.003, 1.012)	0.001
First trimester ^a	None exposure	1.003 (1.002, 1.004)	< 0.001
	Occasional exposure	1.006 (1.005, 1.008)	< 0.001
	Frequent exposure	1.008 (1.004, 1.012)	< 0.001
Second trimester ^a	None exposure	1.003 (1.002, 1.003)	< 0.001
	Occasional exposure	1.005 (1.003, 1.006)	< 0.001
	Frequent exposure	1.004 (1.000, 1.008)	0.069
Third trimester ^a	None exposure	1.002 (1.002, 1.003)	< 0.001
	Occasional exposure	1.005 (1.003, 1.006)	< 0.001
	Frequent exposure	1.005 (1.001, 1.009)	0.007

^aAdjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, multiparity, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, educational level, drinking during pregnancy, and season of delivery.

^bSHS, secondhand smoking.

Table A.1

The interaction between PM2.5 exposure in whole pregnancy and SHS exposure on risk of macrosomia

	Odds Ratio(95%CI)	P value
	whole pregnancy^d	
PM2.5 exposure	1.004 (1.003, 1.005)	< 0.001
Occasional SHS ^a exposure	0.881 (0.757, 1.024)	0.098
Frequent SHS exposure	0.812 (0.537, 1.181)	0.272
Pre-pregnancy BMI	1.035 (1.029, 1.041)	< 0.001
Age at delivery	1.002 (0.997, 1.006)	0.477
Neonate's sex	0.730 (0.706, 0.755)	< 0.001
Multiparity	1.061 (1.016, 1.107)	0.007
Prolonged pregnancy	1.488 (1.353, 1.633)	< 0.001
Season of delivery (Spring)	reference	reference
Season of delivery (Summer)	1.036 (0.982, 1.092)	0.199
Season of delivery (Autumn)	1.050 (1.001, 1.100)	0.045
Season of delivery (Winter)	1.069 (1.023, 1.117)	0.003
Highest education level (Junior high school)	reference	reference
Highest education level (Senior high school)	1.044 (1.000, 1.091)	0.049
Highest education level (college)	1.111 (1.049, 1.175)	< 0.001
Drinking during pregnancy (Never)	reference	reference
Drinking during pregnancy (Quit)	0.980 (0.79, 1.202)	0.852
Drinking during pregnancy (Still)	0.581 (0.406, 0.803)	0.002
Pre-pregnancy diabetes mellitus	1.593 (0.370, 4.377)	0.459

^aSHS, secondhand smoking.^bThe interaction between mean PM2.5 concentration of whole pregnancy and occasional SHS exposure^cThe interaction between mean PM2.5 concentration of whole pregnancy and frequent SHS exposure^dAdjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, multiparity, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, educational level, drinking during pregnancy, and season of delivery.

	Odds Ratio(95%CI)	P value
	whole pregnancy^d	
Pre-pregnancy hypertension	0.838 (0.373, 1.627)	0.637
Family history of diabetes mellitus	1.054 (0.851, 1.291)	0.623
PM2.5 & Occasional SHS exposure ^b	1.002 (1.001, 1.004)	0.010
PM2.5 & Frequent SHS exposure ^c	1.005 (1.000, 1.009)	0.047
^a SHS, secondhand smoking.		
^b The interaction between mean PM2.5 concentration of whole pregnancy and occasional SHS exposure		
^c The interaction between mean PM2.5 concentration of whole pregnancy and frequent SHS exposure		
^d Adjusted for age at delivery, pre-pregnancy BMI, neonatal sex, prolonged pregnancy, multiparity, pre-pregnancy diabetes mellitus, pre-pregnancy hypertension, family history of diabetes mellitus, educational level, drinking during pregnancy, and season of delivery.		

Figures

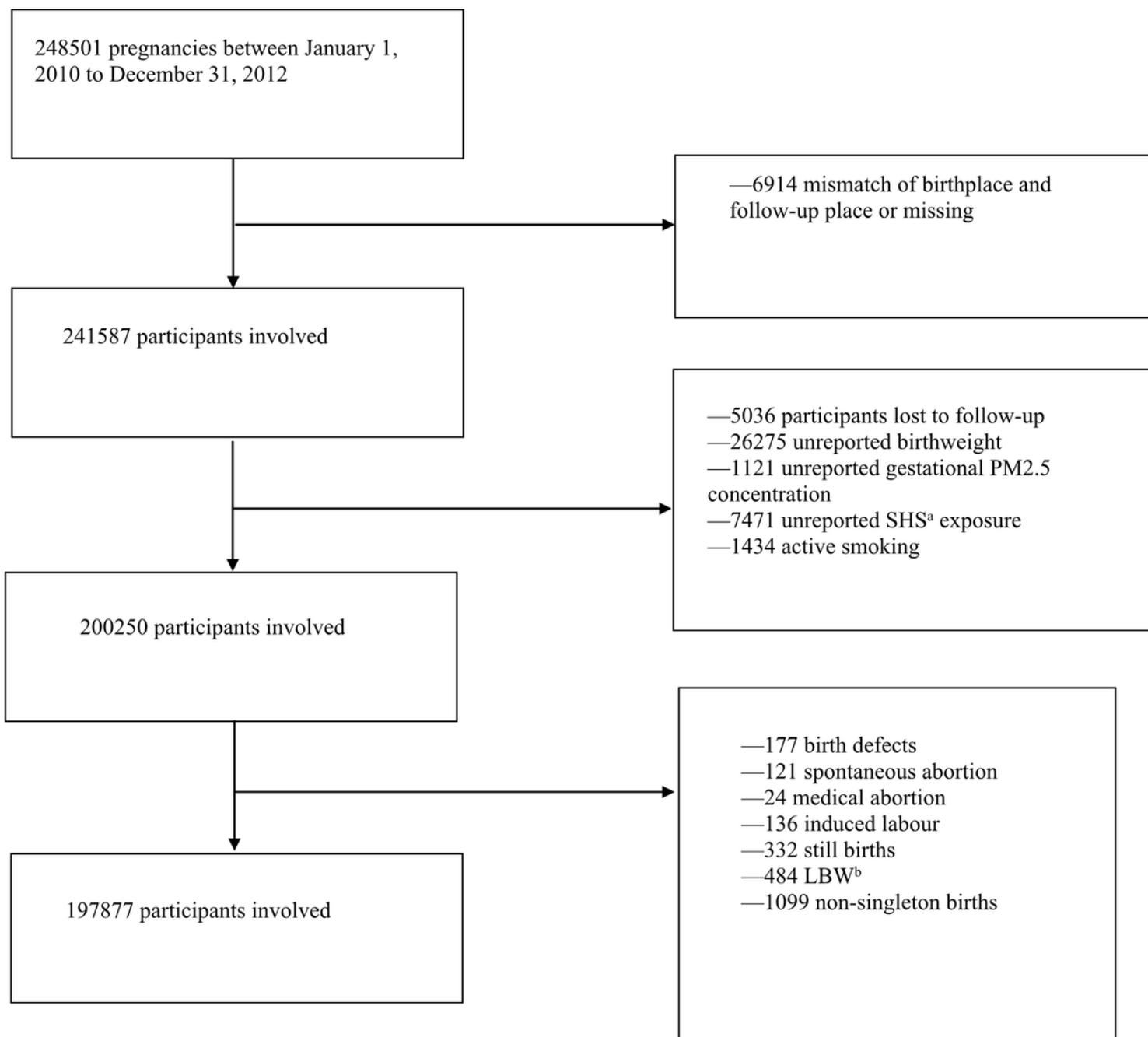


Figure 1

Figure A.1 Flowchart of participants inclusion and exclusion