Science of the Total Environment 880 (2023) 163274

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Third trimester as the susceptibility window for maternal $PM_{2.5}$ exposure and preterm birth: A nationwide surveillance-based association study in China

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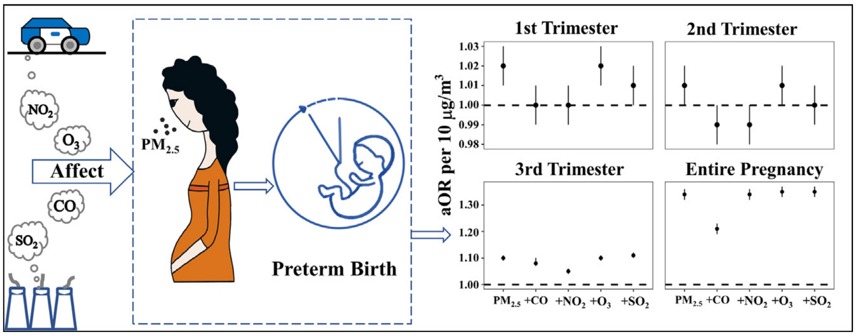
HIGHLIGHTS

- Nationwide study on $PM_{2.5}$ and preterm birth after adjusting for gaseous pollutants.
- Preterm birth is not associated with $PM_{2.5}$ in 1st & 2nd trimesters after adjustment.
- Third trimester is the susceptible window for $PM_{2.5}$ exposure and preterm birth.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Anastasia Paschalidou

Keywords:
Preterm birth
Maternal $PM_{2.5}$ exposure
Susceptible exposure window
Gaseous pollutants

ABSTRACT

Maternal $PM_{2.5}$ exposure has been identified as a potential risk factor for preterm birth, yet the inconsistent findings on the susceptible exposure windows may be partially due to the influence of gaseous pollutants. This study aims to examine the association between $PM_{2.5}$ exposure and preterm birth during different susceptible exposure windows after adjusting for exposure to gaseous pollutants. We collected 2,294,188 records of singleton live births from 30 provinces of China from 2013 to 2019, and the gridded daily concentrations of air pollutants (including $PM_{2.5}$, O_3, NO_2, SO_2, and CO) were derived by using machine learning models for assessing individual exposure. We employed logistic regression to develop single-pollutant models (including $PM_{2.5}$ only) and co-pollutant models (including $PM_{2.5}$ and a gaseous pollutant) to estimate the odds ratio for preterm birth and its subtypes, with adjustment for maternal age, neonatal sex, parity, meteorological conditions, and other potential confounders. In the single-pollutant models, $PM_{2.5}$ exposure in each trimester was significantly associated with preterm birth, and the third trimester exposure showed a stronger association with very preterm birth than that with moderate to late preterm birth. The co-pollutant models revealed that preterm birth might be significantly associated only with maternal exposure to $PM_{2.5}$ in the third

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http://dx.doi.org/10.1016/j.scitotenv.2023.163274
Received 15 December 2022; Received in revised form 17 March 2023; Accepted 31 March 2023

trimester, and not with exposure in the first or second trimester. The observed significant associations between preterm birth and maternal $PM_{2.5}$ exposure in the first and second trimesters in single-pollutant models might primarily be influenced by exposure to gaseous pollutants. Our study provides evidence that the third trimester may be the susceptible window for maternal $PM_{2.5}$ exposure and preterm birth. The association between $PM_{2.5}$ exposure and preterm birth could be influenced by gaseous pollutants, which should be taken into consideration when evaluating the impact of $PM_{2.5}$ exposure on maternal and fetal health.

1. Introduction

Preterm birth, defined as a baby born alive prior to 37 complete weeks of gestation, is associated with an increased risk of neonatal morbidity and mortality (WHO, 1977; Xie et al., 2022). Complications following preterm births are considerable sources of neonatal and under-five mortalities (WHO, 2015). Preterm birth and its complications affect the survival and development of children and impose a heavy burden on individuals, families, and society. According to Global Disease Burden Study, preterm birth caused 664,000 deaths (95 % UI 561,000–789,000) in 2019, making up 13.2 % (12.5–13.9) of deaths for ages under five. It also caused 3.3 % of years lived with disability among children and adolescents (< 20 years) (GBD, 2019). Preterm babies are at a greater risk of long-term adverse health effects such as blindness, hearing loss, cerebral palsy, and depression (Saigal and Doyle, 2008). Worldwide, approximately 15 million babies are born prematurely each year (Walani, 2020). Preterm birth rate also exhibits a rising trend in many developed countries, as well as in some rapidly developing countries like China (Deng et al., 2021). Understanding risk factors for preterm birth is the key to reducing incidence and improving outcome of affected children (Kassebaum et al., 2016). A number of risk factors have been identified including advanced maternal age, active or passive smoking, compromised social status, pregnancy complications, and ambient air pollutants (Cobo et al., 2020). Maternal exposure to ambient air pollutants such as $PM_{2.5}$ could be a risk factor for preterm birth and other adverse pregnancy outcomes, and has received continuous attention from researchers due to inconsistent findings in previous studies (Malley et al., 2017).

Past cohort studies found that $PM_{2.5}$ exposure is associated with an increased risk of preterm birth in several high-income countries (Heo et al., 2019), such as Australia, the United States, and Italy (Chen et al., 2018; Huynh et al., 2006; Ottone et al., 2020). Similar association has been observed in studies conducted in mainland China as well (Cai et al., 2020; Guo et al., 2018; He et al., 2022; Ju et al., 2021; Li et al., 2018a). However, the susceptible exposure windows for $PM_{2.5}$ exposure and preterm birth remain inconclusive. Studies by Cai et al. (2020) and Guo et al. (2018) suggested the strongest association for third trimester $PM_{2.5}$ exposure, while Li et al. (2018a) and He et al. (2022) observed a higher risk for first trimester $PM_{2.5}$ exposure. Despite adjusting for various confounders such as personal characteristics, socioeconomic status, and meteorological conditions in these large sample studies, little attention was paid to the effects of gaseous pollutants. The heterogeneous windows of susceptibility for $PM_{2.5}$ exposure and preterm birth may be affected by unadjusted variables like gaseous pollutants.

Gaseous pollutants may independently or conditionally affect the association between $PM_{2.5}$ exposure and preterm birth. Studies in Spain, Italy, and Australia found a positive association between preterm birth and gaseous pollutant exposure (Chen et al., 2018; Liu et al., 2003; Llop et al., 2010). A recent study in Henan Province, China also identified a positive association between exposure to gaseous pollutants and preterm birth, with the third trimester being suggested as the susceptible exposure window (Zhou et al., 2022). The effect of $PM_{2.5}$ exposure on preterm birth was significant in the single-pollutant model, and the multipollutant model that included NO_2 in addition to $PM_{2.5}$ exposure attenuated the effect on preterm birth (Wang et al., 2018). Other studies included specific single gaseous pollutant into the model, such as SO_2, NO_2, and CO, and observed insignificant associations between $PM_{2.5}$ exposure and preterm birth (Chen et al., 2018; Li et al., 2018b). However, a prospective cohort study in Wuhan, China, demonstrated no effect of the gaseous pollutants (SO_2, NO_2, CO, or O_3) on the relationship between maternal $PM_{2.5}$ exposure and preterm birth (Qian et al., 2016). The inconsistent results obtained so far suggest that the combined effects of exposure to $PM_{2.5}$ and gaseous pollutants on preterm birth still require further investigation.

This study aims (1) to clarify the association between $PM_{2.5}$ exposure and preterm birth during corresponding susceptible exposure window, and (2) to examine the effect of exposure to gaseous pollutants. We utilized gridded daily pollutant concentrations derived from machine learning models to estimate the individual exposure levels of each mother from a nationwide retrospective cohort. We fitted a series of single-pollutant and co-pollutant models to examine the effect of $PM_{2.5}$ exposure in each trimester on preterm birth, and to determine the susceptible window for maternal exposure. In addition, we examined the differed exposure-response associations between $PM_{2.5}$ exposure and preterm birth before and after the implementation of the Universal Two-child Policy (Zeng and Hesketh, 2016). This study is of great value to clarify the susceptible exposure window and to provide evidence for policy making to reduce the health burden from air pollutants exposure and preterm births.

2. Materials and methods

2.1. Cohort information

We collected data from a nationwide singleton live birth cohort from 2013 to 2019 through the China National Population-based Birth Defects Surveillance system (CNPBDS), a network covering hospitals from 30 provinces over China (Fig. 1). The CNPBDS is managed by the National Office of Maternal and Child Health Monitoring (NOMCHM), which monitors the health conditions of women and newborns for public health management. Fetuses and babies are monitored for pregnancy conditions during pregnancy period to 42 days after delivery. In addition, residential addresses also were recorded for each participant and categorized into various residential areas, provinces of residence, and levels of regional economic development. More information about the data collection and quality control can be found in the previous study (Dai et al., 2014).

To accurately assess the exposure of each participant, we specifically collected data on conception dates between January 1, 2013 and June 30, 2019. To control for potential confounding, we excluded records with multiple pregnancies, unknown sex, birth defects, or medically-induced preterm births. In reference to previous studies (Gat et al., 2021; Han et al., 2018), we also excluded records with maternal age > 50 years old. Due to difficulty in obtaining, cases of preeclampsia were not excluded. Our research protocol has been approved by the ethics committee of Sichuan University (NO. K2018075).

2.2. Covariates and outcome variables

We selected birth records with gestational ages ranging from 28 to 45 weeks for the subsequent analyses. In this study, preterm birth was defined as a live birth with gestational age ranging from 28 to < 37 weeks, further divided into the very preterm birth (VPTB; i.e., < 32 gestational weeks) and the moderate to late preterm birth (MPTB; i.e., 32 gestational weeks to < 37 gestational weeks). We considered the following covariates in the statistical analyses, including the neonate sex (male or female), maternal ethnicity (Han or minority), maternal age at delivery (< 20, 20–34, or ≥ 35 years old), parity (first time, second time, or more than two

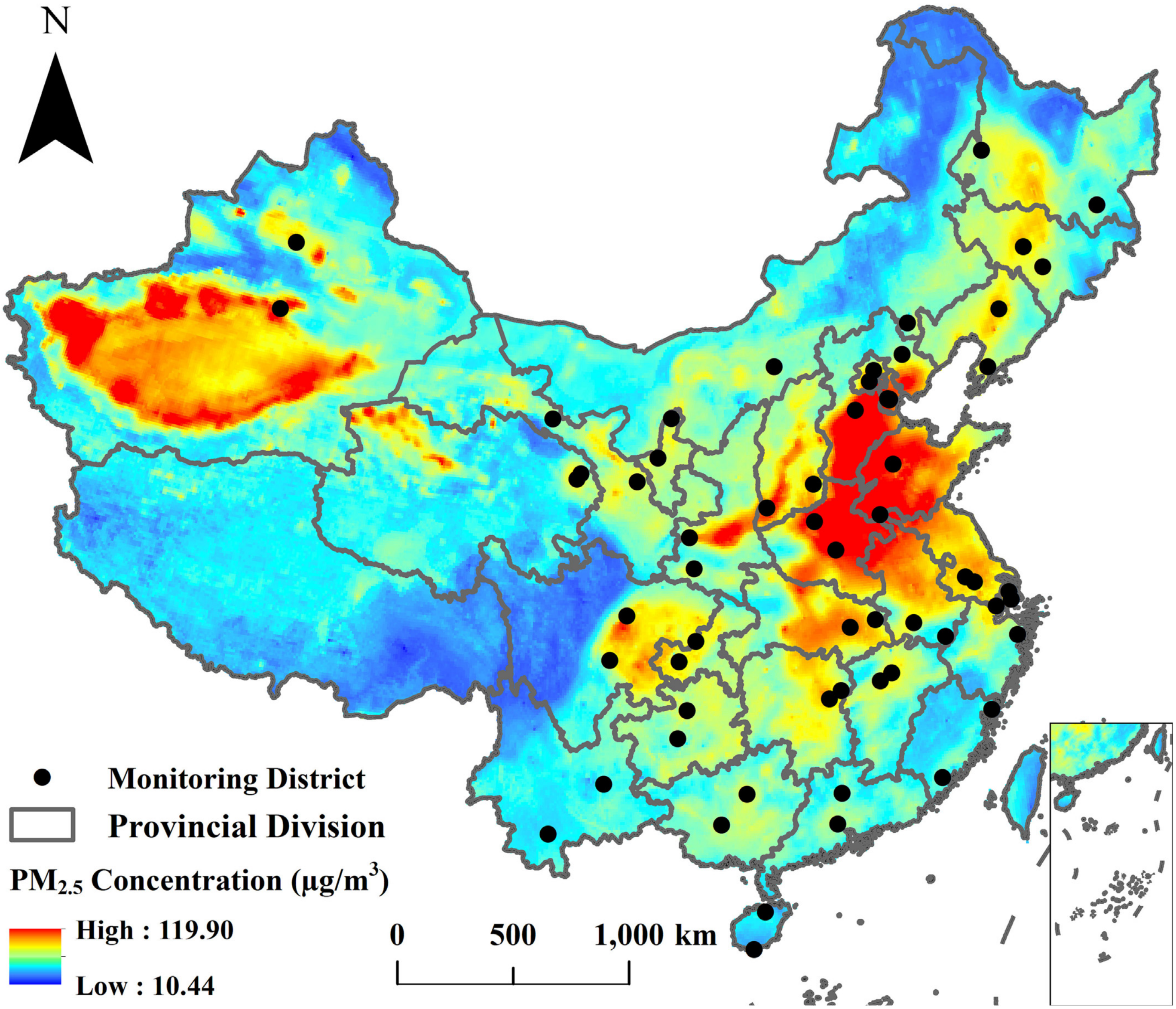

Fig. 1. The distribution of 64 monitoring districts or counties from 30 provinces in China. Please refer to Fig. S1 for the spatial distributions of gaseous pollutant concentrations.

times), the year of conception, the month of conception, the residential status (permanent resident, temporary resident who lived in the area for more than one year, or temporary resident who lived in the area for less than one year), province, residential area (urban or rural), geographic region corresponding to the economic development level (eastern, central, or western). As temperature and relative humidity were found to be associated with preterm birth (Ralphe and Dail, 2018; Ramaswamy et al., 2022), we included them as covariates.

2.3. Assessment of air pollutant exposure

We evaluated the individual exposure levels by matching residential addresses and gestational weeks with the gridded daily air pollutant concentrations and meteorological conditions. This exposure assessment approach was commonly applied in previous studies (Hu et al., 2015; Yan et al., 2021). We geocoded all the birth cases based on their residential addresses recorded in the database. The gridded daily concentrations of $PM_{2.5}$, SO_2, NO_2, CO, and O_3 from January 1, 2013 to December 31, 2019 across China were derived by using the machine learning models based on the data from ground monitoring, satellite retrievals, and various covariates such as meteorological conditions (Liu et al., 2019; Zhan et al., 2018; Zhang et al., 2019). We obtained the site-based observational data of daily temperature and relative humidity from the China Meteorological Administration (CMA, 2019), which were interpolated to the whole nation by using the co-kriging interpolation with elevation (Deutsch and Journel, 1998). The spatial resolution of both air pollutant and meteorological condition data was 10 km. The daily concentrations of air pollutants and meteorological conditions at a higher resolution of 1 km were not available at the time of the study. Only the residential address of the community or village was recorded. For individuals living > 1 km away from the community or village, a resolution of 10 km in exposure assessment may be sufficient to evaluate their individual exposure levels. The average exposure levels of an individual to air pollutants and meteorological conditions in the first trimester (1–13 weeks), second trimester (14–26 weeks), third trimester (27 weeks to birth), and the entire pregnancy were summarized.

2.4. Statistical analyses

To evaluate the associations between preterm birth and $PM_{2.5}$ exposure in each exposure window, we employed the single-pollutant model with multivariate logistic regression to account for the possibility of the outcome variable (Eq. 1).

$$log\ (Y_i) = \alpha + \beta_0 X_i + \beta_1 S_{1i} + \beta_2 S_{2i} + \beta_3 F_i + A_i \times P_i + M_i \times P_i + \varepsilon_i \qquad (1)$$

where Y is the binary outcome variable for preterm birth, i is the ith neonate, and X is the average $PM_{2.5}$ exposure in the first trimester, second trimester, third trimester, and entire pregnancy, respectively. S is three natural cubic splines with 3 degrees of freedom of temperature (S_1), and relative humidity (S_2) to depict the nonlinear effect on preterm birth. F included neonate sex, maternal ethnicity, maternal age, parity, residential status, residential area, and regional economic development level and ε is the residual. We adjusted the models for two interaction terms to control the confounding from the spatial and temporal variations of preterm birth. A is the year of conception, P is the province, and M is the month of conception. The risk of preterm birth was estimated in two subtypes using similar multivariate logistic regression, with full-term births serving as the control group.

We conducted several co-pollutant models for sensitive analyses and stratified analyses.

The co-pollutant models which added a single gaseous pollutant to the single-pollutant model that only included $PM_{2.5}$ exposure were used to examine the robustness of the association between $PM_{2.5}$ exposure and preterm birth. We also estimated the risk of preterm birth in two subtypes using co-pollutant models. To test the differential effect of $PM_{2.5}$ exposure on preterm birth before and after the implementation of the Universal Two-child Policy, we used a stratified model to estimate the association by dividing the study participants into two periods, with July 2016 as the breakpoint marking the implementation of the policy. The Benjamini-Hochberg method was employed to control the false discovery rate (FDR) for various subtypes of preterm birth during multiple tests (Benjamini and Hochberg, 1995). An adjusted P value of < 0.05 was considered statistically significant. The effect of a 10 μg/m^3 increase in $PM_{2.5}$ exposure on preterm birth was quantified using the odds ratio (OR) and 95 % confidence interval (CI). All the statistical analyses were conducted using *R* version 4.1.2 (R Core Team, 2021), with the help of the *"mgcv"* package for logistic regression modeling (Wood, 2017).

3. Results

3.1. Descriptive statistics

Our cohort consisted of 2,294,188 singleton live births from 2013 to 2019 in China, with an average preterm birth rate of 3.61 % (ranging from 3.06 % in 2013 to 5.20 % in 2019). The average rates of very preterm birth and moderate to late preterm birth were 2.62 % and 3.35 %, respectively. For the month of conception, April recorded the highest preterm birth rate (4.20 %) and January recorded the lowest (3.19 %). The preterm birth rate differed considerably among the provinces, with Guangxi province reporting the highest (5.34 %) and Jiangxi province reporting the lowest (1.45 %; Fig. S2). The number of preterm births was higher in the urban areas (63.34 %) than in the rural areas (36.66 %; Table 1). The permanent residents (77.74 %) delivered more preterm babies than the immigrants (22.26 %) did. The number of preterm births delivered by the primiparous mothers was similar to that by the multiparous mothers, which accounted for 52.03 % and 47.97 %, respectively.

Table 2 summarizes the characteristics of the average exposure to air pollutants and meteorological conditions for each exposure window. Among all the individuals in the cohort, the average exposures to air pollutants and meteorological conditions in each trimester were similar to those in the entire pregnancy. Table S1 shows the correlation coefficients among the air pollutants, temperature, and relative humidity in the entire pregnancy (refer to Tables S2–S4 for corresponding correlations in each trimester). For instance, $PM_{2.5}$ exposure was moderately correlated with CO exposure ($r = 0.70$) and weakly correlated with O_3 exposure ($r = 0.34$). The correlations between $PM_{2.5}$ exposures during the three trimesters were weak to moderate, as indicated by the coefficients (Table S5).

Table 1
Descriptive characteristics for a singleton live birth cohort in China during 2013 – 2019.

Characteristics	Preterm (%)	Full-term (%)	All (%)
Maternal ethnicity			
Han	91.06	92.39	92.34
Minority	8.94	7.61	7.66
Maternal age (years old)			
< 20	3.95	3.73	3.74
20–34	77.25	84.25	83.98
≥ 35	18.80	12.02	12.28
Residential area			
Urban	63.34	54.66	54.98
Rural	36.66	45.34	45.02
Regional development level			
Eastern	54.79	48.41	48.64
Central	21.35	26.22	26.05
Western	23.86	25.37	25.31
Parity			
1	52.03	53.68	53.62
2	42.65	41.85	41.90
> 2	5.32	4.47	4.48
Neonate sex			
Male	57.22	52.36	52.54
Female	42.78	47.64	47.46
Year of conception			
2013	13.56	16.11	16.02
2014	13.44	15.30	15.24
2015	15.61	16.50	16.47
2016	18.57	18.31	18.31
2017	17.05	15.54	15.60
2018	16.28	14.49	14.55
2019[a]	5.49	3.75	3.81
Residential status			
Permanent resident	77.74	80.93	80.81
≥ One-year temporary resident	18.68	15.35	15.46
< One-year temporary resident	3.58	3.72	3.73

[a] We assembled a birth cohort based on conception dates ranging from January 1, 2013 to June 30, 2019. The birth count for 2019 was mainly comprised of conceptions from January to March, resulting in a significant decrease in the number of births in that year.

3.2. Exposure-response effects

Based on the single-pollutant models, the association between $PM_{2.5}$ exposure in the third trimester and preterm birth (aOR = 1.10, 95%CI: 1.09–1.11) was stronger than those in the first trimester (aOR = 1.02, 95%CI: 1.01–1.03) and second trimester (aOR = 1.01, 95%CI: 1.00–1.02; Fig. 2). Due to the cumulative effect, $PM_{2.5}$ exposure in the entire pregnancy associated with an increased risk of preterm birth (aOR = 1.34, 95%CI: 1.32–1.36). We found a stronger association of $PM_{2.5}$ exposure in the third trimester with VPTB (aOR = 1.32, 95%CI: 1.27–1.36) than with MPTB (aOR = 1.09, 95%CI: 1.08–1.10). The aOR of VPTB related to $PM_{2.5}$ exposure in the third trimester was higher than those in the first and second trimesters. There was an insignificant association between VPTB and $PM_{2.5}$ exposure in the first trimester (aOR = 1.02, 95%CI: 0.99–1.06; $P = 0.20$), and between MPTB and $PM_{2.5}$ exposure in the second trimester (aOR = 1.01, 95%CI: 1.00–1.02; $P = 0.10$). The significant associations between $PM_{2.5}$ exposure and preterm birth, including its two subtypes, remained unchanged after controlling for FDR correction (Tables S6–9).

The results of the co-pollutant models show that exposure to $PM_{2.5}$ in the third trimester was significantly associated with preterm birth, but exposure in the first or second trimester was not, after adjusting for exposure to SO_2, NO_2, or CO (Fig. 2). The association between $PM_{2.5}$ exposure in the third trimester and preterm birth was attenuated after adjusting for exposure to NO_2 (aOR = 1.05, 95%CI: 1.04–1.06) or CO (aOR = 1.08, 95% CI: 1.07–1.10), but intensified after adjusting for SO_2 exposure (aOR =

Table 2
The distribution of the average exposures to air pollutants and meteorological conditions in each exposure period.

Variable	First trimester	Second trimester	Third trimester	Entire pregnancy
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
$PM_{2.5}$ (μg/m^3)	52.46 (23.35)	50.22 (23.21)	59.98 (23.34)	50.88 (18.43)
SO_2 (μg/m^3)	23.02 (18.80)	21.79 (18.16)	21.42 (18.14)	22.07 (14.78)
NO_2 (μg/m^3)	33.48 (14.51)	32.82 (14.39)	33.10 (14.35)	33.12 (12.50)
O_3 (μg/m^3)	86.19 (34.98)	86.05 (35.37)	84.23 (35.26)	85.51 (25.69)
CO (mg/m^3)	0.95 (0.35)	0.93 (0.34)	0.93 (0.34)	0.94 (0.27)
Temperature (°C)	16.06 (9.01)	16.80 (9.15)	16.44 (9.15)	16.44 (5.41)
Relative humidity (%)	70.52 (12.87)	70.95 (12.68)	70.89 (12.63)	70.79 (11.12)

1.11, 95%CI: 1.10–1.12). However, the association between preterm birth and $PM_{2.5}$ exposure in the first and second trimesters was substantially attenuated after adjusting for exposure to SO_2, NO_2, or CO, and became statistically insignificant ($P > 0.05$). In addition, the adjustment for O_3 exposure posed negligible effects on the association between preterm birth and $PM_{2.5}$ exposure in any trimester. For $PM_{2.5}$ exposure in the entire pregnancy, the risk of preterm birth increased after adjusting for exposure to SO_2 (aOR = 1.35, 95%CI: 1.33–1.37), NO_2 (aOR = 1.34, 95%CI: 1.32–1.36), CO (aOR = 1.21, 95%CI: 1.19–1.23), or O_3 (aOR = 1.35, 95%CI: 1.33–1.37).

Based on the co-pollutant models, $PM_{2.5}$ exposure in the third trimester was significantly associated with the increased risks of VPTB and MPTB (Fig. 2). The association between $PM_{2.5}$ exposure in the third trimester and VPTB was intensified after adjusting for exposure to SO_2 (aOR = 1.38, 95%CI: 1.33–1.43) or O_3 (aOR = 1.33, 95%CI: 1.28–1.38) and was attenuated after adjusting for exposure to NO_2 (aOR = 1.22, 95%CI: 1.17–1.27) or CO (aOR = 1.30, 95%CI: 1.24–1.35). For $PM_{2.5}$ exposure in the second trimester, the association with VPTB became insignificant after adjusting for exposure to NO_2 or CO ($P > 0.05$). In addition, the adjustment for SO_2 exposure intensified the association between $PM_{2.5}$ exposure in the third trimester and MPTB (aOR = 1.10, 95%CI: 1.09–1.11), while the adjustment for exposure to NO_2 (aOR = 1.04, 95%CI: 1.03–1.06) or CO (aOR = 1.07, 95%CI: 1.06–1.08) attenuated the association. We found no significant association between $PM_{2.5}$ exposure in the first trimester and MPTB after adjusting for exposure to SO_2, NO_2, or CO ($P > 0.05$).

3.3. Analyses on the Universal Two-child Policy

Table 3 summarizes the effect estimates of the associations between $PM_{2.5}$ exposure and preterm birth before and after the implementation of the Universal Two-child Policy. Based on the single-pollutant models, the association of $PM_{2.5}$ exposure in the third trimester with preterm birth was attenuated, with aOR of 1.18 (95%CI: 1.16–1.19) and 1.08 (95% CI: 1.06–1.09) for the conceptions before and after implementing the policy, respectively. According to the co-pollutant models, we found substantial attenuation of the association between $PM_{2.5}$ exposure in the third trimester and preterm birth after implementing the policy. The change pattern of aOR after implementing the policy was also revealed for $PM_{2.5}$ exposure in the entire pregnancy. Nevertheless, the aOR for $PM_{2.5}$ exposure in the first and second trimesters exhibited inconsistent change patterns. For instance, the association between $PM_{2.5}$ exposure in the first trimester and preterm birth was attenuated to be statistically insignificant after implementing the policy in the single-pollutant models. After adjusting for SO_2 exposure, $PM_{2.5}$ exposure in the second trimester and preterm birth retained an insignificant association after implementing the policy.

4. Discussion

We found a significant association between $PM_{2.5}$ exposure in each trimester and preterm birth based on single-pollutant models. After adjusting

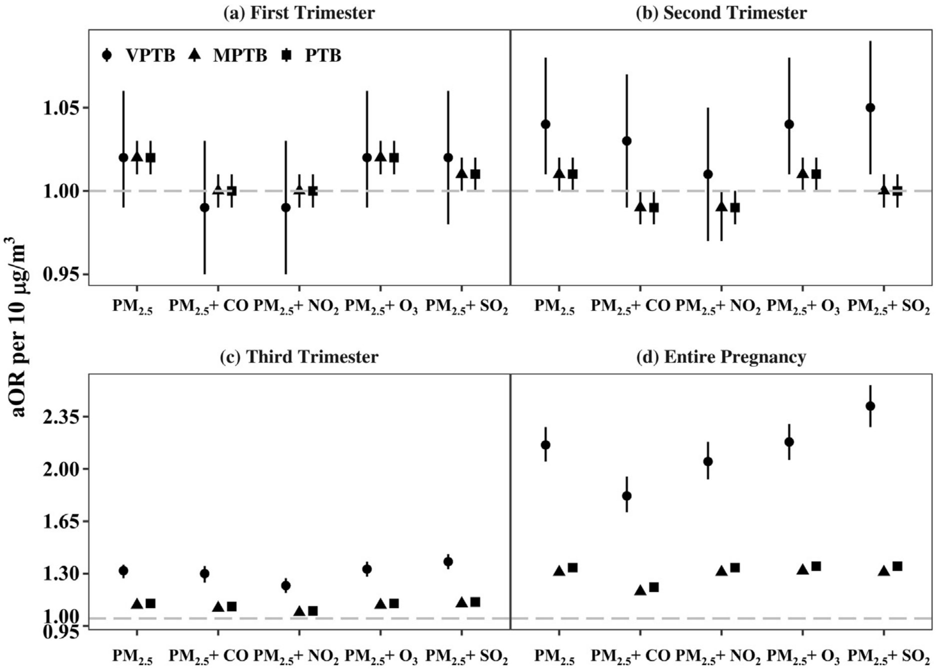

Fig. 2. The adjusted odds ratio (aOR) and 95 % confidence interval (CI) of very preterm birth (VPTB), moderate to late preterm birth (MPTB), and preterm birth (PTB) related to a 10 μg/m^3 increase in $PM_{2.5}$ exposure before and after adjusting for gaseous pollutants in the (a) first trimester, (b) second trimester, (c) third trimester, and (d) entire pregnancy.

Table 3
The adjusted odds ratio (aOR) and 95 % confidence interval (CI) of preterm birth associated with a 10 μg/m^3 increase in $PM_{2.5}$ exposure with different subgroups.

Pollutants	Universal Two-child Policy	First trimester	Second trimester	Third trimester	Entire pregnancy
$PM_{2.5}$	NO	1.03 (1.02, 1.05)*	1.01 (1.00, 1.02)	1.18 (1.16, 1.19)*	1.45 (1.42, 1.48)*
	YES	1.00 (0.98, 1.01)	1.02 (1.00, 1.03)*	1.08 (1.06, 1.09)*	1.32 (1.29, 1.34)*
+ SO_2	NO	1.02 (1.01, 1.04)*	1.01 (0.99, 1.02)	1.19 (1.17, 1.21)*	1.48 (1.45, 1.51)*
	YES	0.99 (0.97, 1.00)	1.01 (0.99, 1.02)	1.07 (1.06, 1.09)*	1.31 (1.28, 1.34)*
+ NO_2	NO	1.02 (1.00, 1.04)*	1.00 (0.98, 1.01)	1.12 (1.11, 1.14)*	1.45 (1.42, 1.48)*
	YES	0.96 (0.94, 0.97)*	0.98 (0.97, 1.00)*	1.02 (1.00, 1.03)*	1.33 (1.30, 1.36)*
+ O_3	NO	1.05 (1.03, 1.06)*	1.01 (1.00, 1.03)*	1.15 (1.13, 1.17)*	1.43 (1.40, 1.46)*
	YES	1.00 (0.98, 1.01)	1.02 (1.00, 1.03)*	1.09 (1.07, 1.11)*	1.34 (1.31, 1.37)*
+ CO	NO	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	1.17 (1.15, 1.19)*	1.31 (1.28, 1.35)*
	YES	0.97 (0.95, 0.98)*	1.00 (0.98, 1.02)	1.04 (1.02, 1.05)*	1.15 (1.12, 1.18)*

* $P < 0.05$.

for exposure to gaseous pollutants, the association between $PM_{2.5}$ exposure in the first and second trimesters and preterm birth became insignificant, but remained significant for the third trimester. The effect of $PM_{2.5}$ exposure in the third trimester on VPTB was stronger than on MPTB. The significant association between $PM_{2.5}$ exposure in the third trimester and preterm birth was attenuated after the implementation of the Universal Two-child Policy. Previous studies have indicated that the third trimester is the susceptible exposure window for maternal $PM_{2.5}$ exposure and preterm birth, which was consistent with our results (Cai et al., 2020; Liang et al., 2019). Due to the moderate correlation between $PM_{2.5}$ and gaseous pollutants exposure, gaseous pollutants might influence the association between $PM_{2.5}$ exposure and preterm birth. Despite a decline in $PM_{2.5}$ exposure levels, it is crucial to mitigate $PM_{2.5}$ exposure in the third trimester to lower the risk of preterm birth.

The birth cohort from a population-based sample had a lower rate of preterm birth compared to the hospital-based sample (Song et al., 2022). Our study reported a preterm birth rate of 3.6 % from 2013 to 2019, which was lower than the rate of 6.1 % reported by Deng et al. (2021) based on the National Maternal Near Miss Surveillance Systems (NMNMSS) from 2012 to 2018. We had a similar range of maternal ages. We excluded mothers aged over 50, following the selection criteria for maternal age in previous literature (Gat et al., 2021; Han et al., 2018), and including mothers over 50 did not alter the association between $PM_{2.5}$ exposure and preterm birth (Table S10). The difference in preterm birth rate can be attributed to two factors. Firstly, the 6.1 % rate included both singleton and multiple pregnancies, while our study only included singleton pregnancies. Secondly, the data source of NMNMSS is primarily high-level referral hospitals in urban areas, which have a higher risk of preterm birth. Our study, on the other hand, collected data from a nationwide singleton live birth cohort through the China National Population-based Birth Defects Surveillance system, with participants recruited randomly and with less selection bias.

Toxicological and epidemiological studies suggest that $PM_{2.5}$ exposure can lead to oxidative stress, pulmonary and placental inflammation, blood coagulation, changes in endothelial function, and alterations in hemodynamic responses (Kannan et al., 2006). Two possible mechanisms might explain why the third trimester is a susceptible window to $PM_{2.5}$ exposure. $PM_{2.5}$-induced placental inflammation has been linked to shorter gestational periods in mice exposed to $PM_{2.5}$ during the latter half of gestation (Blum et al., 2017). In addition, $PM_{2.5}$ exposure may impact thyroid hormones, which play a role in stimulating fetal growth during the latter half of gestation (Yuan et al., 2020). However, the precise biological mechanisms behind $PM_{2.5}$ exposure and preterm birth have yet to be fully understood, and more research is needed to explore potential ways that could mitigate the impact of $PM_{2.5}$ exposure on preterm birth.

The association of preterm birth with $PM_{2.5}$ exposure in the first and second trimesters was found to be insignificant after adjusting for exposure to gaseous pollutants (including NO_2, SO_2, and CO), which might refine the results from previous nationwide studies that may have overlooked the effects of gaseous pollutants (Guo et al., 2018; He et al., 2022; Li et al., 2018a). We found similar effects of gaseous pollutants, which was consistent with the previous studies (Guo et al., 2020; Jo et al., 2019; Pan et al., 2017). The previous significant association of preterm birth with $PM_{2.5}$ exposure in the first and second trimesters may have been due to the lack of adjustment for gaseous pollutant exposure, which was consistent with our single-model results. However, $PM_{2.5}$ and gaseous pollutants have some shared sources of pollution (Liu et al., 2022b; Shi et al., 2021). The seasonal pattern of $PM_{2.5}$ and some gaseous pollutants was found to be similar and linked to meteorological conditions such as temperature and wind speed (Chen et al., 2019). The elevated risk of preterm birth was correlated with exposure to both $PM_{2.5}$ and gaseous pollutants (Chen et al., 2018). The estimate of the association between $PM_{2.5}$ exposure and preterm birth could be distorted if the effects of gaseous pollutants were not adjusted (Qian et al., 2016). We found that the significant associations of $PM_{2.5}$ exposure in the first and second trimesters with preterm birth might be primarily affected by gaseous pollutant exposure (Tables S11–S12). The association between $PM_{2.5}$ exposure in the third trimester and preterm birth remained significant even after adjusting for gaseous pollutant exposure, indicating that the third trimester is a susceptible window of $PM_{2.5}$ exposure. Based on the multi-pollutant models, we found that the third trimester remained the only susceptible exposure window of $PM_{2.5}$ (Fig. S3). Considering potentially severe collinearity among the air pollutants, the estimates of the multi-pollutant models were of high uncertainty (Bouma et al., 2023; Kalkbrenner et al., 2018; Qian et al., 2016). Our study corroborates the possible influence of gaseous pollutants on the association between $PM_{2.5}$ exposure and preterm birth (Liu et al., 2018). Adjusting for gaseous pollutant exposure is crucial when assessing the association between $PM_{2.5}$ exposure and preterm birth (Samet et al., 2000).

We found a stronger positive association between $PM_{2.5}$ exposure in the third trimester and VPTB compared to MPTB, suggesting a need to decrease $PM_{2.5}$ exposure in pregnant women to reduce the risk of VPTB. Previous studies found that the effects of maternal $PM_{2.5}$ exposure on preterm birth were stronger for VPTB than MPTB (Wang et al., 2018; Zhang et al., 2020). Maternal $PM_{2.5}$ exposure may trigger preterm birth by stimulating inflammation, leading to acceleration of placental aging (Basu et al., 2017). VPTB and MPTB are affected by similar risk factors such as particulate matter, but VPTB is more vulnerable (Qiu et al., 2014), which may account for the stronger association between $PM_{2.5}$ exposure and VPTB. VPTB is associated with higher rates of necrotizing enterocolitis and bronchopulmonary dysplasia, causing higher initial hospital care costs (Korvenranta et al., 2010; Stoll et al., 2015). Moreover, very-preterm babies require more healthcare and have higher longer-term costs in childhood compared to non-VPTB peers (Klitkou et al., 2017). Effective healthcare measures to mitigate maternal $PM_{2.5}$ exposure, particularly in the third trimester, are critical to lower the risk of VPTB.

To the best of our knowledge, the impact of $PM_{2.5}$ exposure on preterm birth before and after the Universal Two-child Policy had rarely been investigated. We found that the association of $PM_{2.5}$ exposure in the third trimester with preterm birth was attenuated after implementing the policy, which may be caused by the decrease in toxic constituents in $PM_{2.5}$. The concentrations of heavy metals (Cd and Zn) in $PM_{2.5}$ were found to be significantly associated with the shortened gestational weeks (Zhang et al., 2016). The following mechanisms may explain the significant association between heavy metal exposure and preterm birth. Excessive exposure to heavy metals can result in the accumulation in pregnant women, causing oxidative stress and disruptive of hormonal functioning (Anand et al., 2019; Danzeisen et al., 2007; Pollack et al., 2014). In recent years, the concentrations of heavy metal elements such as Pb, Cd, and Zn in $PM_{2.5}$ showed a decreasing trend in China (Liu et al., 2022a), which might explain the relatively milder effects of $PM_{2.5}$ exposure on preterm birth. The Universal Two-child Policy was associated with a rise in the preterm birth rate, which also implied existence of unadjusted confounders. Further comprehensive research is needed to fully understand the policy's impact on preterm birth.

The advantages of our study are as follows: Firstly, to the best of our knowledge, it is the largest retrospective cohort study on the association between preterm birth and $PM_{2.5}$ exposure in China in terms of sample size, it covers a wide spatial area and a long observation period. Secondly, we used machine learning models to predict daily concentrations with high-spatial-resolution data for exposure assessment. Thirdly, unlike previous nationwide studies in China that focused on the association between $PM_{2.5}$ exposure and preterm birth, we specifically investigated the impact of gaseous pollutants on the association. Finally, we examined the susceptible exposure window and the effect of the Universal Two-child Policy on the association.

Several limitations need to be considered in our study. Firstly, we did not have information on indoor exposure levels of the study populations, as women spend > 80 % of their time indoors (Duan et al., 2013), and pregnant women may spend more time inside than the general population (Nethery et al., 2009). As a result, ambient exposure assessment alone may not accurately reflect individual pollutant exposure (Xu et al., 2022). Secondly, our study did not account for confounders such as maternal smoking status, vitamin status, heavy metals, and pregnancy complications such as preeclampsia, which could lead to uncertainty in the relationship between $PM_{2.5}$ exposure and preterm birth. Vitamin status information was difficult to collect for a large cohort, and previous research has shown conflicting findings regarding its association with preterm birth (Iams et al., 2008). The use of vitamin supplements by pregnant women in China has risen from 2013 to 2017, with a 6.5 % increase in the number of pregnant women using multiple supplements in Beijing, and > 70 % pregnant women in Sichuan used vitamin supplements from 2014 to 2016 (Bian et al., 2021; Han et al., 2022). Public understanding of nutritional supplements was improved through nutrition education (Bian et al., 2021). Incorporating vitamin status into models could have a minor effect on the relationship between $PM_{2.5}$ exposure and preterm birth. Heavy metals, such as lead, arsenic, mercury, and cadmium, present in the environment, induce oxidative stress in the placenta and increase the risk of preterm birth (Khanam et al., 2021; Singh et al., 2020). Evaluating heavy metal exposure in pregnant women requires samples from maternal blood, urine, umbilical cord blood, and amniotic fluid (Khanam et al., 2021), which can be challenging in a large cohort study. The effect of preeclampsia on preterm birth was partially adjusted for variables such as maternal age and parity, however, information on preeclampsia was not available for the national cohort. Preeclampsia shares common risk factors with preterm birth, such as maternal age and parity, and may mediate the association between preterm birth and advanced maternal age (Nawsherwan et al., 2020). Considering this is a large cohort study, including cases of preeclampsia may have limited impact on the estimated effect of $PM_{2.5}$ exposure on preterm birth. Maternal smoking is a source of $PM_{2.5}$ exposure, with rates of 11 to 13 % in high-income countries (Ion and Bernal, 2014), but low during pregnancy in China (Kong et al., 2008).

The correlation between maternal exposure at different stages of pregnancy could potentially lead to a founding bias in determining the susceptible exposure window for preterm birth. In our study, the correlations between $PM_{2.5}$ exposure during different windows are weak to moderate (Table S5). By following a previous study that considered the hysteresis effect (Bell et al., 2007), we regressed $PM_{2.5}$ (and each gaseous pollutant) exposure in the third trimester on exposure in the first and second trimesters. A similar approach was applied to $PM_{2.5}$ (and each gaseous pollutant) exposure in the second trimester. The residuals were used in the single-pollutant and co-pollutant models to evaluate the effect of $PM_{2.5}$ exposure on preterm birth for controlling the hysteresis effect. The results show that the third trimester remained the only susceptible exposure window, while the aOR slightly decreased (Fig. S4). Therefore, the founding bias due to the correlations between $PM_{2.5}$ exposure during different exposure windows might have a limited effect on the results.

5. Conclusions

The large cohort study included more than two million participants to evaluate the association between $PM_{2.5}$ exposure and preterm birth on the nationwide level. Our results suggest that the third trimester is the susceptible exposure window of $PM_{2.5}$ exposure on preterm birth, especially on very preterm birth. However, after adjusting for exposure to gaseous pollutants, we found no significant association between preterm birth and $PM_{2.5}$ exposure in the first and second trimesters, which expands our understanding of the impact of multi-pollutant exposure on preterm birth. For the first time, we also found that the significant association between $PM_{2.5}$ exposure and preterm birth was attenuated after the implementation of the Universal Two-child Policy. It is important to note that recently implemented Three-child Policy may lead to an increase in preterm birth, and more research is needed to understand the long-term health effects of exposure to $PM_{2.5}$ and gaseous-pollutant exposures for pregnant women and newborns.

CRediT authorship contribution statement

ZQ and WL drafted the manuscript. ZQ, WL, WX, and YQ performed data cleaning and statistical analyses. ZC, YG, ZL, MJ, FY, and QL provided extensive comments on this manuscript. YZ, YQ, LD, and HL revised the manuscript. HL, YZ, and LD designed the research plan and revised the manuscript. All authors had read and approved the manuscript.

Data availability

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research is supported in part by the National Key Research and Development Program (2017YFC0211705), Key Research and Development Program of Sichuan Province (2019YFS0409), and the National Natural Science Foundation of China (22076129).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163274.

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