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*CORRESPONDENCE
Hao Ying
stephenying_2011@163.com
Jing Cai
jingcai@fudan.edu.cn
Yan Zhao
zy861201@163.com

†These authors have contributed
equally to this work and share first
authorship
‡These authors have contributed
equally to this work and share last
authorship

Prenatal exposure to fine particulate matter and the risk of spontaneous preterm birth: A population-based cohort study of twins

Ping Qiao[1†], Kechen Fan[2†], Yirong Bao[1†], Ling Yuan[1], Haidong Kan[3], Yan Zhao[4*‡], Jing Cai[3*‡] and Hao Ying[1,4*‡]

[1]Departments of Obstetrics, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai, China, [2]Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai, China, [3]Key Lab of Public Health Safety of the Ministry of Education and National Health Commission Key Laboratory of Health Technology Assessment, School of Public Health, Fudan University, Shanghai, China, [4]Shanghai Key Laboratory of Maternal Fetal Medicine, Shanghai, China

Background: Studies in singletons have suggested that prenatal exposure to fine particulate matter ($PM_{2.5}$) and some of its chemical components is associated with an increased risk of preterm birth (PTB). However, no study has been conducted in twins.

Purpose: To examine the associations of maternal exposure to total $PM_{2.5}$ mass and its carbonaceous components with PTB in twin pregnancies.

Methods: A total of 1,515 pairs of twins and their mothers were enrolled from a previous twin birth cohort that had been conducted at the Shanghai First Maternity and Infant Hospital School of Medicine of Tongji University in China. Participants who had iatrogenic PTBs were excluded. Maternal exposure to total $PM_{2.5}$ mass and two carbonaceous components, namely, organic carbon (OC) and black carbon (BC), was estimated by a satellite-based model. The associations between $PM_{2.5}$ exposure and the risk of spontaneous PTB were evaluated by logistic regression analysis.

Results: This study found that exposure to total $PM_{2.5}$ mass and OC during the second trimester of pregnancy was significantly associated with an increased risk of spontaneous PTB. An interquartile range (IQR) increase in total $PM_{2.5}$ mass and OC exposure during the second trimester was associated with 48% (OR = 1.48, 95% CI, 1.06, 2.05) and 50% (OR = 1.50, 95% CI, 1.00, 2.25) increases in the odds of PTB, respectively. However, no significant association was found between BC exposure during any exposure window and the risk of PTB.

Conclusion: The findings suggest that exposure to ambient air pollution with fine particles may be a risk factor for spontaneous PTB in twin pregnancies. The middle stage of pregnancy seems to be a critical window for the impacts of $PM_{2.5}$ exposure on PTB in twin pregnancies.

Introduction

With the extensive development of assisted reproductive technology (ART) and delayed childbearing age, the incidence of twin pregnancy has dramatically increased worldwide (1–3). The prevalence of twin pregnancy has been reported to be 3.26% in the U.S. population (4). The latest statistics involving 556,298 births from 64 different levels of Chinese medical care showed that the incidence of twin pregnancy was 3.69% in the Chinese population, showing an upward trend (5). Twin pregnancies have all the complications of singleton pregnancies but at higher rates, especially preterm birth (PTB). The incidence of PTB among twin pregnancies is as high as 60%, which is more than 6–10 times higher than that among singleton pregnancies (4).

PTB is a major public health challenge, with its complications accounting for an estimated 35% of 3.1 million annual neonatal deaths worldwide (6). It not only influences early-life outcomes but is also associated with an increased risk of cerebral palsy, long-term neurodevelopmental impairment, and metabolic and cardiovascular diseases, which places a heavy financial and spiritual burden on affected families as well as societies (7). It is therefore crucial to identify potential modifiable risk factors, which is of great importance to public health.

Fine particulate matter ($PM_{2.5}$), which refers to particulate matter that is $<2.5\,\mu m$ in aerodynamic diameter, is the most serious environmental threat worldwide. It is a complex mixture comprising various components. Several studies in singleton pregnancies have shown that prenatal exposure to $PM_{2.5}$ and some of its chemical components, such as carbonaceous species (8, 9), is responsible for the increased risk of PTB (10–13). However, the effect of $PM_{2.5}$ exposure on spontaneous PTBs in twin pregnancies remains unknown.

It is more challenging to investigate the effects of $PM_{2.5}$ on multiple preterm births because the etiology is more complex and varied. Furthermore, because of the inadequate sample size, insights that are specific to multiple gestations cannot be obtained. Tracking "medically indicated" (defined as an elective cesarean section or induced labor before 37 weeks of gestation due to maternal complications or fetal indications, which is also called "iatrogenic") (14) vs. "non-indicated" provider-initiated PTBs would be crucial, but definitions and data are missing, and

this distinction is not readily available at the national level or consistently over time, even in developed countries.

Therefore, the purpose of this study was to investigate the associations between maternal exposure to $PM_{2.5}$ and its carbonaceous components and spontaneous PTB in a twin birth cohort in Shanghai, China, by maximizing the control for a variety of potential confounders.

Methods

Study population

Participants in the present study were from a previous twin birth cohort that had been conducted at the Shanghai First Maternity and Infant Hospital School of Medicine of Tongji University in China. The recruitment and eligibility criteria have been described in detail and are as follows. Briefly, twin pregnancies delivered after 24 weeks of gestation and with two liveborn infants were included in the cohort. The original cohort excluded twin pregnancies with genetic or structural abnormalities of either fetus, monochorionic twin pregnancies complicated by twin-twin transfusion syndrome (TTTS) or twin anemia-polycythemia sequence (TAPS), pregnancies with multifetal pregnancy reduction (MFPR), and pregnancies with a known history of chronic hypertension, diabetes, and immunological or kidney disease before the pregnancy. A total of 2,122 twin pregnancies were included in the cohort between January 2013 and June 2016. In the present study, participants who had iatrogenic PTBs ($N = 402$) and who were not locally living in the city of Shanghai ($N = 205$) were excluded. This resulted in a final analysis of 1,515 pairs of twins and their mothers. The study protocols were approved by the Ethics Committee of the Shanghai First Maternity and Infant Hospital.

Data collection and outcome definitions

Data on residential addresses, maternal age (MA), prepregnancy height and weight, gravidity and parity, and the use of ART were collected during each participant's first prenatal visit (before 16 weeks of gestation). Data on twin chorionicity, intrauterine treatment, pregnancy complications, such as pregnancy-associated hypertensive disorders, gestational diabetes mellitus (GDM), TTTS, and selective fetal growth restriction (sFGR), were obtained from obstetric records, which were completed by midwives and obstetricians. Twin birth outcomes, including the gestational age (GA), mode of delivery, Apgar score, birth weight, birth length, and sex, were abstracted from newborn discharge records. The outcome of interest in the present study was PTB, which was generally defined as a delivery occurring before 37 weeks of gestation. GA was calculated based on a pregnant woman's last menstrual period (LMP) and was

confirmed or corrected by ultrasound measurement of the crown-rump length (CRL) in the first trimester of pregnancy. Chorionicity was confirmed by determining the number of gestational sacs between $6 + 0$ and $9 + 0$ weeks and the lambda and T signs between $11 + 0$ and $13 + 6$ weeks of gestation (15).

PM$_{2.5}$ exposure assessment

Individual exposure to total PM$_{2.5}$ mass and its 2 carbonaceous constituents during pregnancy were assessed based on each participant's residential address. The 2 carbonaceous constituents were organic carbon (OC) and black carbon (BC), which have been associated with an increased risk of PTB in singleton pregnancies. Data were calculated for four exposure windows for each participant: the entire period of pregnancy, first trimester (0–90 days) of pregnancy, second trimester (91–180 days) of pregnancy and third trimester of pregnancy (day 181 of pregnancy to delivery) based on monthly concentrations of PM$_{2.5}$.

The concentrations of total PM$_{2.5}$ mass and its chemical constituents during the study period were derived from a satellite-based model. The exposure assessment model was from the V4.CH.02 product of the Atmospheric Composition Analysis Group (ACAG), which extends the approach of van Donkelaar et al. (16) to provide ground-level predictions of total PM$_{2.5}$ and its main chemical constituents, including over China. Specifically, this model combines multiple satellite products of aerosol optical depth (AOD) retrievals and determines ground-level PM$_{2.5}$ concentrations based on total mass and the simulated geophysical relationship between PM$_{2.5}$ and AOD. The model for China was built using ground monitoring data from ∼1,000 monitors at a monthly timescale with a 1×1 km resolution, resulting in an overall R^2 of 0.78, vs. using cross-validated ground-based monitors over China. GEOS-Chem simulation was applied to partition the total PM$_{2.5}$ mass into several compositions.

The time resolution of the PM$_{2.5}$ exposure data was monthly. If a pair of twins was born in the middle of 1 month, their trimester-specific exposures were calculated according to a time-weighted method. Briefly, if the conception date was on day Dj of month Mi, the first month of pregnancy ended 30 days later, which was approximately Dj of month Mi+1. Then, the concentration of the first month (Con. 1st month) was calculated according to the following equation:

$$\text{Con. } (1^{\text{st}} \text{ month}) = \frac{(30 - D_j)/30 \times \text{Con. } M_i + D_j/30 \times \text{Con. } M_{i+1}}{2}$$

The first trimester covered the first 3 months (90 days) of pregnancy, and the concentrations of the first trimester were calculated as the mean exposure of the first 3 months. Then,

the exposure levels of the second and third trimesters were calculated accordingly.

Statistical analysis

The general characteristics of the participants are presented as percentages (%) and were compared between PTB cases and term birth control cases using the χ^2 test. The PM$_{2.5}$ exposure levels were not normally distributed, and medians (25th, 75th percentile) are presented to characterize their distribution. The potential differences in PM$_{2.5}$ exposure levels between PTB cases and term birth control cases were compared by means of the Mann–Whitney U-test.

The associations between PM$_{2.5}$ exposure and the risk of PTB were evaluated by logistic regression analysis using odds ratios (ORs) as the risk measure, with 95% confidence intervals (CIs). MA, parity, prepregnancy body mass index (BMI), gestational hypertension disorders, GDM, the use of ART, twin chorionicity, twin growth discordance and birth seasons were adjusted in the logistic regression models. These covariates were included because of data accessibility and their associations with the exposure or outcomes. To further explore the exposure-response relationships between PM$_{2.5}$ exposure and the risk of PTB, exposure levels to total PM$_{2.5}$ mass or each chemical constituent were categorized into quartiles and estimated ORs for each quartile with the first quartile as a reference. The P-value for trend was estimated by including the categorized exposure data as continuous variables.

Sensitivity analyses were subsequently conducted to examine the impacts of gestational hypertensive disorders and GDM on the associations between PM$_{2.5}$ exposure and PTB. All logistic regression analyses were replicated and restricted to participants without gestational hypertension disorders or GDM. All statistical analyses were performed using SPSS 16.0 (SPSS, Chicago, IL), and a two-sided $P < 0.05$ was considered statistically significant.

Results
Population characteristics

Table 1 presents the general characteristics of the participants. The majority of the participating women were nulliparous (81.5%), aged <35 years (78.1%), and conceived naturally (73.3%). Among the 1,515 pairs of twins, the incidence of PTB was 50.4% (764/1,515). The PTB group and term birth group differed in the use of ART, twin chorionicity and the incidence of gestational hypertension. Results of the χ^2 test showed that there were no significant differences in MA ($P = 0.205$), parity ($P = 0.812$), prepregnancy BMI ($P = 0.080$),

TABLE 1 General characteristics of the study population.

Characteristics	Total, n (%) N = 1,515	PTB, n (%) N = 764	Non-PTB, n (%) N = 751	p-value[a]
Maternal age (years)				
<35	1,183 (78.1)	607 (79.5)	576 (76.7)	0.205
≥35	332 (21.9)	157 (20.5)	175 (23.3)	
Prepregnancy BMI (kg/m^2)				
<18.5	92 (6.1)	50 (6.5)	42 (5.6)	0.080
18.5–24.9	1,028 (67.9)	498 (65.2)	530 (70.6)	
≥25	395 (26.1)	216 (28.3)	179 (23.8)	
The use of ART				
Yes	404 (26.7)	179 (23.4)	225 (30.0)	0.004**
No	1,111 (73.3)	585 (76.6)	526 (70.0)	
Parity				
Nulliparous	1,235 (81.5)	621 (81.3)	614 (81.8)	0.812
Multiparous	280 (18.5)	143 (18.7)	137 (18.2)	
Twin chorionicity				
Dichorionic	1,174 (77.5)	473 (61.9)	701 (93.3)	0.000**
Monochorionic	341 (22.5)	291 (38.1)	50 (6.7)	
Season of delivery[a]				
Spring	498 (32.9)	262 (34.3)	236 (31.4)	0.653
Summer	338 (22.3)	166 (21.7)	172 (22.9)	
Autumn	265 (17.5)	134 (17.5)	131 (17.4)	
Winter	414 (27.3)	202 (26.4)	212 (28.2)	
GDM				
Yes	344 (22.7)	168 (22.0)	176 (23.4)	0.502
No	1,171 (77.3)	596 (78.0)	575 (76.6)	
Gestational hypertension				
Yes	268 (17.7)	212 (27.7)	56 (7.5)	0.000**
No	1,247 (82.3)	552 (72.3)	695 (92.5)	

[a]p-values were calculated by the χ^2-test. **p < 0.01.

the season of delivery ($P = 0.653$), or the incidence of GDM ($P = 0.502$) between the two groups.

PM$_{2.5}$ exposure levels

The distributions of exposure levels to total PM$_{2.5}$ mass and its 2 carbonaceous constituents, namely, OC and BC, during the whole pregnancy and each trimester are shown in Table 2. The exposure levels to total PM$_{2.5}$ mass, OC and BC varied across pregnancy trimesters. During the whole pregnancy, the median exposure levels to total PM$_{2.5}$ mass, OC and BC were 52.50, 9.23, and 3.59 μg/m^3, respectively. The correlations between exposure to total PM$_{2.5}$ mass, OC and BC for each trimester and the whole pregnancy are shown in Supplementary Table 1. The results showed that the exposure levels to total PM$_{2.5}$ mass, OC and BC were highly correlated with each other, with correlation coefficients ranging from 0.83 to 0.96.

Analyses of potential differences in PM$_{2.5}$ exposure levels between the PTB and term birth groups were conducted using the Mann–Whitney U-test. The results showed that total PM$_{2.5}$ mass exposure during the second trimester was significantly higher in the PTB group than in the term birth group (53.50 vs. 51.75 μg/m^3, respectively, $P = 0.013$). No significant difference was found for OC or BC exposure between the two groups (Table 2).

Association between PM$_{2.5}$ exposure and PTB risk

Table 3 shows the associations between total PM$_{2.5}$ mass exposure, carbonaceous constituent exposure and the risk of PTB. Only total PM$_{2.5}$ mass exposure during the second trimester was significantly associated with an increased risk of PTB. In the adjusted model, an interquartile range (IQR; 16.5

TABLE 2 Descriptive statistics of air pollution exposure levels ($\mu g/m^3$).

	Total	PTB	Non-PTB	p-value[a]
$PM_{2.5}$				
Trimester 1	49.25 (42.00, 57.00)	48.75 (42.00, 56.75)	49.75 (42.00, 57.50)	0.388
Trimester 2	52.50 (44.50, 61.00)	53.50 (45.00, 61.75)	51.75 (44.00, 60.25)	0.013*
Trimester 3	53.00 (45.67, 61.25)	53.00 (45.67, 60.75)	53.25 (45.67, 61.50)	0.822
Entire pregnancy	52.50 (49.67, 54.56)	52.56 (49.56, 54.78)	52.40 (49.78, 54.33)	0.565
OC				
Trimester 1	5.70 (4.40, 12.25)	5.73 (4.40, 12.14)	5.67 (4.40, 12.42)	0.729
Trimester 2	8.27 (4.88, 14.05)	8.44 (4.91, 14.43)	8.05 (4.85, 13.67)	0.075
Trimester 3	8.28 (4.90, 14.22)	8.03 (4.90, 14.05)	8.40 (4.93, 14.27)	0.778
Entire pregnancy	9.23 (8.21, 9.98)	9.30 (8.11, 10.13)	9.18 (8.23, 9.88)	0.208
BC				
Trimester 1	3.15 (2.80, 4.00)	3.15 (2.80, 3.95)	3.15 (2.80, 4.05)	0.661
Trimester 2	3.52 (2.97, 4.35)	3.55 (3.00, 4.40)	3.50 (2.93, 4.30)	0.091
Trimester 3	3.45 (2.95, 4.33)	3.43 (2.97, 4.30)	3.52 (2.93, 4.33)	0.913
Entire pregnancy	3.59 (3.32, 3.76)	3.59 (3.29, 3.77)	3.58 (3.35, 3.74)	0.703

[a]p-values were calculated by the Mann–Whitney U-test. *p < 0.05.

TABLE 3 Associations of total $PM_{2.5}$ mass and exposure to two carbon constituents with the risk of preterm birth.

Exposure time window	ORs (95 CI%) Adjusted model[a]		
	$PM_{2.5}$ total mass	OC	BC
Trimester 1	0.84 (0.67, 1.06)	0.85 (0.64, 1.14)	0.83 (065, 1.07)
Trimester 2	1.48 (1.06, 2.05)*	1.50 (1.00, 2.25)*	1.40 (0.99, 2.00)
Trimester 3	0.79 (0.60, 1.05)	0.73 (0.52, 1.04)	0.73 (0.51, 1.04)
Entire pregnancy	0.95 (0.81, 1.11)	0.93 (0.79, 1.09)	0.94 (0.79, 1.13)

[a]Models adjusted for MA, prepregnancy BMI, gestational hypertension disorders, GDM, the use of ART, parity, twin chorionicity, twin growth discordance, and birth season. *p < 0.05.

$\mu g/m^3$) increase in total $PM_{2.5}$ mass exposure during the second trimester was associated with a 48% (OR = 1.48, 95% CI, 1.06, 2.05) increase in the odds of PTB.

Similar to total $PM_{2.5}$ mass exposure, OC exposure during the second trimester was found to be significantly associated with an increased risk of PTB. For an IQR (9.17 $\mu g/m^3$) increase in OC exposure during the second trimester, the odds of PTB increased by 50% (OR = 1.50, 95% CI, 1.00, 2.25). However, no significant association was found between BC exposure during any exposure window and PTB.

Given that the PTB risk was significantly positively correlated with total $PM_{2.5}$ mass or OC exposure during the second trimester of pregnancy, the exposure-response relationships of $PM_{2.5}$ exposure with PTB risk were further explored by categorizing the distribution of total $PM_{2.5}$ mass or each chemical constituent exposure into quartiles. As shown in

Figure 1, significant positive associations with the risk of PTB were observed for total $PM_{2.5}$ mass exposure, with a monotonic linear increase in ORs across quartiles (P for trend = 0.008).
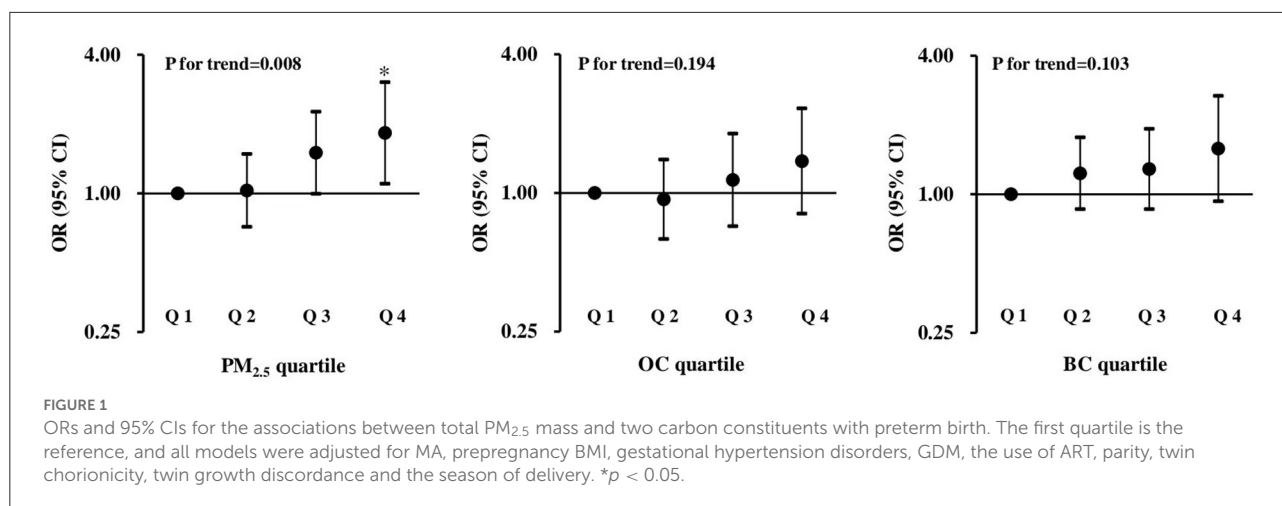
Sensitivity analyses

To exclude the impacts of gestational hypertensive disorders and GDM on the associations between $PM_{2.5}$ exposure and PTB, the regression analysis was restricted to participating women without gestational hypertensive disorders or GDM. As shown in Supplementary Table 2, the associations of total $PM_{2.5}$ mass and OC exposure during the second trimester with PTB were not appreciably changed.

Discussion

In this study, the associations of maternal exposure to total $PM_{2.5}$ mass and its carbonaceous components (OC and BC) with the risk of spontaneous PTB in twin pregnancies were examined. Exposure to total $PM_{2.5}$ mass and OC during the second trimester of pregnancy was associated with an increased risk of PTB. The results suggest that maternal exposure to $PM_{2.5}$ may be a risk factor contributing to PTB in twin pregnancies.

Most previous studies have reported significant associations between $PM_{2.5}$ exposure and an increased risk of PTB in singletons, despite the heterogeneity in study designs and $PM_{2.5}$ exposure assessment methods (17–20). For example, in a retrospective cohort study including 231,637 births, Basu et al. found a 16.4% increase in the odds of PTB

FIGURE 1
ORs and 95% CIs for the associations between total PM$_{2.5}$ mass and two carbon constituents with preterm birth. The first quartile is the reference, and all models were adjusted for MA, prepregnancy BMI, gestational hypertension disorders, GDM, the use of ART, parity, twin chorionicity, twin growth discordance and the season of delivery. *$p < 0.05$.

per IQR increase in PM$_{2.5}$ exposure during the whole pregnancy (9). In another study, using data from 183 individual countries, Mallry et al. estimated that the percentage of PTB attributed to PM$_{2.5}$ exposure was 18% (21). The reasons for the increased incidence of PTB in twin pregnancies are multifactorial and include maternal complications, such as preeclampsia and intrahepatic cholestasis of pregnancy, and fetal complications, which are unique to twin pregnancies and directly related to chorionicity. Spontaneous PTB of multiple gestations may also have unique predisposing factors, including a short cervical length, uterine hypertonicity or distension, intrauterine infection or inflammation (22). Studies have shown that PM$_{2.5}$ has the ability to activate multiple pathophysiological processes, including oxidative stress, DNA damage, immunological alteration and inflammation (23, 24). PM$_{2.5}$ can potentially be deposited deep into the lungs and may enter the circulatory system, which may induce systemic inflammation, or enter the placenta through simple diffusion (25). The direct toxic effects of PM$_{2.5}$ on placental inflammation (26) may potentially result in altered placental vascular function (27), triggering the occurrence of PTB. In addition, PM$_{2.5}$ may affect placental vasoconstriction, interfering with placental oxygen and nutrient transport and leading to fetal hypoxia and PTB (28). A larger placental mass is associated with increased secretion of mediators, such as corticotrophin-releasing hormone (CRH), which is correlated with the onset of parturition (22). In the present study of spontaneous PTB, a 48% (OR = 1.48, 95% CI, 1.06, 2.05) increase in the odds of PTB was found to be associated with an IQR increase in total PM$_{2.5}$ mass, and the estimated effect seemed to be larger than that in singletons. Possible reasons may be that a greater twin placental mass leads to increased placental inflammatory responses to PM$_{2.5}$ and increased CRH secretion. Further studies are warranted to understand the biological mechanisms of PM$_{2.5}$-induced PTB.

The observed positive associations of OC and PM$_{2.5}$ exposure with PTB risk in twins were consistent with the data of a previous study conducted on singletons (29). Shanghai is a city with relatively serious organic carbon air pollution, and Xu et al. identified that biomass burning from the adjacent Yangtze River Delta region was responsible for the high OC plumes during the harvest season (30). Bové et al. reported that BC could pass through the placenta and accumulate on the fetal side of the placenta, which may represent a potential mechanism that leads to the occurrence of preterm birth (31). Previous studies conducted among singletons also reported significant associations between prenatal BC exposure and an increased risk of preterm birth (28, 32, 33). In this study, the associations of prenatal BC exposure with PTB risk were marginally significant, with an OR of 1.40 (95% CI, 0.99, 2.00). The magnitude and direction of the associations were generally similar to those of OC exposure with PTB. The lack of significant associations might be due to the lower exposure levels of BC (mean exposure level of BC, 3.59 $\mu g/m^3$; mean exposure level of OC, 9.23 $\mu g/m^3$) and the relatively small sample size of this study.

Identifying critical exposure windows would allow for the design of targeted prevention strategies, as well as the exploration of the potential biological mechanisms underlying the associations of PM$_{2.5}$ exposure with PTB. In previous research evaluating the effect of gestational PM$_{2.5}$ exposure on pregnancy complications of placental origin, the critical window was identified as the first trimester (34). In this study, PM$_{2.5}$ exposure during the second trimester demonstrated significant associations with PTB, which is consistent with some previous epidemiological studies (35–37), whereas other studies identified the late stage of pregnancy as the most significant critical window (19, 20, 38). This window of susceptibility (the second trimester) was considered to be biologically plausible because Mayer's study showed that from the second trimester, fetal-placental blood flow starts to increase continuously with

advancing gestation to meet the increasing fetal demand for oxygen and nutrients (39), which in turn leads to elevated fetal exposure to endogenous and exogenous factors such as an inhalational dose of ambient $PM_{2.5}$ and maternal systemic inflammatory mediators (40).

Strengths

This study extends previous epidemiological research on air pollution and PTB in singletons and suggests that maternal exposure to $PM_{2.5}$ during the second trimester is an important risk factor for PTB in twin pregnancies. The strengths of the study included the relatively large sample size of twins and the ability to control for a variety of potential confounders, such as MA, prepregnancy BMI, the use of ART, parity, twin chorionicity, twin growth discordance and the season of delivery and maternal pregnancy complications. The use of administrative databases improved the ability to distinguish spontaneous from medically indicated births, which makes this study on $PM_{2.5}$ and spontaneous PTB in twin pregnancies more scientific by excluding provider-initiated PTB for maternal or complex twin indications.

Limitations

However, several limitations should be considered. First, all participants with twin pregnancies were recruited from a hospital-based birth cohort, which was subject to an inevitable selection bias and limited the generalizability of the results. Second, although comprehensive confounders were considered in the data analysis, some known influencing factors of PTB, such as maternal education level, occupation, sleep status during pregnancy, passive smoking, and socioeconomic and nutritional status, were unavailable in the analysis; thus, residual confounding was possible Third, the exposure assessment mainly relied upon exposure at the maternal residence and ignored the mobility of each participant between their residence and workplace, which may cause exposure misclassification. However, the study by Pereira et al. indicated that maternal residential mobility had only a slight or even no impact on the direction of the effect estimate (41). Fourth, information on possible treatments to prevent recurrent PTB, such as progesterone, pessary, or cerclage, was not available in the selected studies. Finally, this was only an observational study, and the biological mechanisms underlying the association of $PM_{2.5}$ exposure with PTB need to be further investigated. Although we tried our best to comprehensively collect as many covariates as possible, future research with a larger sample size and more optimized research design is still needed to verify the phenomenon in the future.

Conclusion

It was found that maternal exposure to total $PM_{2.5}$ mass and OC during the second trimester of pregnancy was associated with an increased risk of PTB in twin pregnancies. These findings suggest that exposure to $PM_{2.5}$ during the middle stage of pregnancy may have a role in the etiology of PTB. Further studies are necessary to confirm the findings.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the dataset generated during and/or analyzed during the current study are not publicly available due to ethics reason. Requests to access these datasets should be directed to zzybbmm@aliyun.com.

Ethics statement

The study protocols were approved by the Ethics Committee of the Shanghai First Maternity and Infant Hospital (No. KS18118). This was a retrospective study. All data were extracted from the medical records and were anonymized, and no written consent was obtained from the participating pregnant women.

Author contributions

PQ: conceptualization, investigation, and writing-original draft preparation. KF: software and formal analysis. YB and LY: data curation. HK: supervision. YZ: validation, software, and formal analysis. JC: methodology, software, and formal analysis. HY: conceptualization, project administration, supervision, and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Smits J, Monden C. Twinning across the developing world. *PLoS ONE.* (2011) 6:e25239. doi: 10.1371/journal.pone.0025239

2. Young BC, Wylie BJ. Effects of twin gestation on maternal morbidity. *Semin Perinatol.* (2012) 36:162–8. doi: 10.1053/j.semperi.2012.02.007

3. Piccoli GB, Arduino S, Attini R, Parisi S, Fassio F, Biolcati M, et al. Multiple pregnancies in CKD patients: an explosive mix. *Clin J Am Soc Nephrol.* (2013) 8:41–50. doi: 10.2215/CJN.02550312

4. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: final data for 2018. *Natl Vital Stat Rep.* (2019) 68:1–47. Available online at: https://stacks.cdc.gov/view/cdc/82909

5. Wei J, Liu C, Cui H, Zhang L, Chen J, Liu S, et al. Diagnosis, treatment and health care guidelines for preterm birth in twin pregnancy (2020 edition). *Chin J Prac Gynecol Obstetrics.* (2020) 36:949–56. doi: 10.19538/j.fk2020100111

6. Liu L, Johnson H, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet.* (2012) 379:2151–61. doi: 10.1016/S0140-6736(12)60560-1

7. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet.* (2012) 379:2162–72. doi: 10.1016/S0140-6736(12)60820-4

8. Cai J, Zhao Y, Kan J, Chen R, Martin R, van Donkelaar A, et al. Prenatal exposure to specific PM2.5 chemical constituents and preterm birth in china: a nationwide cohort study. *Environ Sci Technol.* (2020) 54:14494–501. doi: 10.1021/acs.est.0c02373

9. Basu R, Pearson D, Ebisu K, Malig B. Association between PM2.5 and PM2.5 constituents and preterm delivery in California, 2000-2006. *Paediatr Perinat Epidemiol.* (2017) 31:424–34. doi: 10.1111/ppe.12380

10. Sun Z, Yang L, Bai X, Du W, Shen G, Fei J, et al. Maternal ambient air pollution exposure with spatial-temporal variations and preterm birth risk assessment during 2013-2017 in Zhejiang Province, China. *Environ Int.* (2019) 133(Pt B):105242. doi: 10.1016/j.envint.2019.105242

11. Guo T, Wang Y, Zhang H, Zhang Y, Zhao J, Wang Q, et al. The association between ambient PM2.5 exposure and the risk of preterm birth in China: a retrospective cohort study. *Sci Total Environ.* (2018) 633:1453–9. doi: 10.1016/j.scitotenv.2018.03.328

12. Smith RB, Beevers SD, Gulliver J, Dajnak D, Fecht D, Blangiardo M, et al. Impacts of air pollution and noise on risk of preterm birth and stillbirth in London. *Environ Int.* (2020) 134:105290. doi: 10.1016/j.envint.2019.105290

13. Klepac P, Locatelli I, Korošec S, Künzli N, Kukec A. Ambient air pollution and pregnancy outcomes: a comprehensive review and identification of environmental public health challenges. *Environ Res.* (2018) 167:144–59. doi: 10.1016/j.envres.2018.07.008

14. Goldenberg RL, Gravett MG, Iams J, Papageorghiou AT, Waller SA, Kramer M, et al. The preterm birth syndrome: issues to consider in creating a classification system. *Am J Obstet Gynecol.* (2012) 206:113–8. doi: 10.1016/j.ajog.2011.10.865

15. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. *Ultrasound Obstet Gynecol.* (2016) 47:247–63. doi: 10.1002/uog.15821

16. van Donkelaar A, Martin RV, Li C, Burnett RT. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. *Environ Sci Technol.* (2019) 53:2595–611. doi: 10.1021/acs.est.8b06392

17. Chang HH, Warren JL, Darrow LA, Reich BJ, Waller LA. Assessment of critical exposure and outcome windows in time-to-event analysis with application to air pollution and preterm birth study. *Biostatistics.* (2015) 16:509–21. doi: 10.1093/biostatistics/kxu060

18. Hao H, Chang HH, Holmes HA, Mulholland JA, Klein M, Darrow LA, et al. Air pollution and preterm birth in the U.S. State of Georgia (2002-2006): associations with concentrations of 11 ambient air pollutants estimated by combining community multiscale air quality model (CMAQ) simulations with stationary monitor measurements. *Environ Health Perspect.* (2016) 124:875–80. doi: 10.1289/ehp.1409651

19. Lavigne E, Yasseen AS 3rd, Stieb DM, Hystad P, van Donkelaar A, Martin RV, et al. Ambient air pollution and adverse birth outcomes: differences by maternal comorbidities. *Environ Res.* (2016) 148:457–66. doi: 10.1016/j.envres.2016.04.026

20. DeFranco E, Moravec W, Xu F, Hall E, Hossain M, Haynes EN, et al. Exposure to airborne particulate matter during pregnancy is associated with preterm birth: a population-based cohort study. *Environ Health.* (2016) 15:6. doi: 10.1186/s12940-016-0094-3

21. Malley CS, Kuylenstierna JC, Vallack HW, Henze DK, Blencowe H, Ashmore MR. Preterm birth associated with maternal fine particulate matter exposure: a global, regional and national assessment. *Environ Int.* (2017) 101:173–82. doi: 10.1016/j.envint.2017.01.023

22. Stock S, Norman J. Preterm and term labour in multiple pregnancies. *Semin Fetal Neonatal Med.* (2010) 15:336–41. doi: 10.1016/j.siny.2010.06.006

23. Chen G, Knibbs LD, Zhang W, Li S, Cao W, Guo J, et al. Estimating spatiotemporal distribution of PM1 concentrations in China with satellite remote sensing, meteorology, and land use information. *Environ Pollut.* (2018) 233:1086–94. doi: 10.1016/j.envpol.2017.10.011

24. Filep Á, Fodor GH, Kun-Szabó F, Tiszlavicz L, Rázga Z, Bozsó G, et al. Exposure to urban PM1 in rats: development of bronchial inflammation and airway hyperresponsiveness. *Respir Res.* (2016) 17:26. doi: 10.1186/s12931-016-0332-9

25. Vadillo-Ortega F, Osornio-Vargas A, Buxton MA, Sánchez BN, Rojas-Bracho L, Viveros-Alcaráz M, et al. Air pollution, inflammation and preterm birth: a potential mechanistic link. *Med Hypotheses.* (2014) 82:219–24. doi: 10.1016/j.mehy.2013.11.042

26. Saenen ND, Vrijens K, Janssen BG, Madhloum N, Peusens M, Gyselaers W, et al. Placental nitrosative stress and exposure to ambient air pollution during gestation: a population study. *Am J Epidemiol.* (2016) 184:442–9. doi: 10.1093/aje/kww007

27. Backes CH, Nelin T, Gorr MW, Wold LE. Early life exposure to air pollution: how bad is it? *Toxicol Lett.* (2013) 216:47–53. doi: 10.1016/j.toxlet.2012.11.007

28. U.S. EPA. *Integrated ScienceAssessment (ISA) for Particulate Matter (Final Report, Dec 2009).* Washington, DC: U.S. EnvironmentalProtection Agency(2009).

29. Laurent O, Hu J, Li L, Kleeman MJ, Bartell SM, Cockburn M, et al. A statewide nested case-control study of preterm birth and air pollution by source and composition: California, 2001-2008. *Environ Health Perspect.* (2016) 124:1479–86. doi: 10.1289/ehp.1510133

30. Xu J, Wang Q, Deng C, McNeill VF, Fankhauser A, Wang F, et al. Insights into the characteristics and sources of primary and secondary organic carbon: high time resolution observation in urban Shanghai. *Environ Pollut.* (2018) 233:1177–87. doi: 10.1016/j.envpol.2017.10.003

31. Bové H, Bongaerts E, Slenders E, Bijnens EM, Saenen ND, Gyselaers W, et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun.* (2019) 10:3866. doi: 10.1038/s41467-019-11654-3

32. Riddell CA, Goin DE, Morello-Frosch R, Apte JS, Glymour MM, Torres JM, et al. Hyper-localized measures of air pollution and risk of preterm birth in Oakland and San Jose, California. *Int J Epidemiol.* (2022) 50:1875–1885. doi: 10.1093/ije/dyab097

33. Fang J, Yang Y, Zou X, Xu H, Wang S, Wu R, et al. Maternal exposures to fine and ultrafine particles and the risk of preterm birth from a retrospective study in Beijing, China. *Sci Total Environ.* (2022) 812:151488. doi: 10.1016/j.scitotenv.2021.151488

34. Michikawa T, Morokuma S, Yamazaki S, Takami A, Sugata S, Yoshino A, et al. Exposure to chemical components of fine particulate matter and ozone, and placenta-mediated pregnancy complications in Tokyo: a register-based study. *J Expo Sci Environ Epidemiol.* (2022) 32:135–45. doi: 10.1038/s41370-021-00299-4

35. Sheridan P, Ilango S, Bruckner TA, Wang Q, Basu R, Benmarhnia T. Ambient fine particulate matter and preterm birth in California: identification of critical exposure windows. *Am J Epidemiol.* (2019) 188:1608–15. doi: 10.1093/aje/kwz120

36. Wang Q, Benmarhnia T, Zhang H, Knibbs LD, Sheridan P, Li C, et al. Identifying windows of susceptibility for maternal exposure to ambient air pollution and preterm birth. *Environ Int.* (2018) 121(Pt 1):317–24. doi: 10.1016/j.envint.2018.09.021

37. Liu X, Ye Y, Chen Y, Li X, Feng B, Cao G, et al. Effects of prenatal exposure to air particulate matter on the risk of preterm birth and roles of maternal and cord blood LINE-1 methylation: a birth cohort study in Guangzhou, China. *Environ Int.* (2019) 133(Pt A):105177. doi: 10.1016/j.envint.2019.105177

38. Yuan L, Zhang Y, Wang W, Chen R, Liu Y, Liu C, et al. Critical windows for maternal fine particulate matter exposure and adverse birth outcomes: the Shanghai birth cohort study. *Chemosphere.* (2020) 240:124904. doi: 10.1016/j.chemosphere.2019.124904

39. Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. *Ultrasound Obstet Gynecol.* (2013) 41:136–45. doi: 10.1002/uog.11204

40. Wu H, Jiang B, Zhu P, Geng X, Liu Z, Cui L, et al. Associations between maternal weekly air pollutant exposures and low birth weight: a distributed lag nonlinear model. *Environ Res Lett.* (2018) 13:024023. doi: 10.1088/1748-9326/aaa346

41. Pereira G, Bracken MB, Bell ML. Particulate air pollution, fetal growth and gestational length: the influence of residential mobility in pregnancy. *Environ Res.* (2016) 147:269–74. doi: 10.1016/j.envres.2016.02.001