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Associations of Prenatal Exposures to Fine Particulate Matter and Its Compositions with Preterm Birth Risk in Twins

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Abstract

Twin pregnancies have a higher risk of preterm birth (PTB) than single pregnancies, but studies about prenatal air pollution exposure and PTB in twin pregnancies are still scarce. To explore associations of prenatal fine particulate matter ($PM_{2.5}$) exposure with PTB in twins, we collected birth data from 21 hospitals across China. Data on $PM_{2.5}$ and its compositions (NO_3^-, BC, NH_4^+, SO_4^{2-}, and OM) were collected from Tracking Air Pollution. Generalized linear models were used to examine associations of air pollution with PTB. Each IQR increment in $PM_{2.5}$, NH_4^+, SO_4^{2-}, NO_3^-, BC, and OM during entire pregnancy, the OR (95% CI) were 1.46 (1.34–1.59), 1.54 (1.39–1.70), 1.34 (1.25–1.44), 1.44 (1.30–1.59), 1.28 (1.20–1.37), and 1.28 (1.18–1.38), respectively. The results of trimester-specific analyses followed the patterns as seen during the entire pregnancy (all $p < 0.05$). The *PAF* of PTB attributable to $PM_{2.5}$ was 40.75% (95% CI: 32.5%, 48.26%) in the total population. Participants living in warmer regions and lower residential greenness were more susceptible to $PM_{2.5}$. Our findings suggest pregnant women should avoid severe air pollution exposure throughout pregnancy. Reducing heat exposure and increasing green spaces in communities can reduce PTB risk.

Keywords: $PM_{2.5}$; chemical composition; prenatal exposure; preterm birth; twins

1. Introduction

Preterm birth (PTB) is a significant negative birth outcome that can greatly affect children's health. Preterm birth (PTB), characterized as live births occurring before 37 completed weeks of gestation [1,2], represents a worldwide challenge and is an increasingly pressing issue within the population. In 2020, the estimated global prevalence

of PTB reached 13.4 million, representing 9.9% of all births worldwide [3]. Meanwhile, the estimated prevalence of PTB in China was reported to be 752,900 (6.1%) in 2020, ranking fourth in the world [3]. In addition, PTB is recognized as a significant risk factor for neonatal mortality (children under five), and has been related to short-term and long-term health effects, such as adverse effects on health and growth, cognitive and mental disabilities, as well as an increased likelihood of chronic diseases later in life [4–6]. Each year, around 1 million infants lose their lives as a result of complications associated with preterm birth [1]. Consequently, identifying the risk factors associated with PTB and minimizing its occurrence is crucial for public health.

One of the potential risk factors is prenatal air pollution exposure. Prior research indicates that $PM_{2.5}$ exposure may elevate the risk of PTB [2,7]. However, findings regarding the connection between $PM_{2.5}$ pollution and PTB have shown variability [7–9]. For example, a multicenter investigation conducted in China found a link between $PM_{2.5}$ exposure and an increased risk of PTB [7]. In contrast, Sabah et al. reported no correlation between prenatal $PM_{2.5}$ exposure and PTB in their analysis of data from multiple cities in the United States [8]. The disparities of the results may be due to the variation in the composition and concentration of $PM_{2.5}$ [10,11]. For example, in $PM_{2.5}$ chemical compositions, the annual level of SO_4^{2-} and NH_4^+ are higher in Eastern U.S. than in Western U.S. (29% vs. 12% and 11% vs. 8%), while the annual concentration of NO_3^- was higher in Western U.S. than in Eastern U.S. (17% vs. 11%) [12]. In China, the levels of NO_3^-, SO_4^{2-}, and NH_4^+ are higher in Northern than Southern, with proportions of 31.6%, 15.8%, and 13.2% in Northern and 27.2%, 13.3% and 13.2% in Southern, respectively [13]. Determining the specific components of $PM_{2.5}$ that negatively impact the risk of PTB is crucial for developing effective prevention strategies.

However, most evidence regarding the link between $PM_{2.5}$ and its components with PTB originates from research focused on singleton births. As assisted reproductive technology (ART) continues to advance, the global rate of twin pregnancies has risen to approximately 4% [14], and risks of negative birth outcomes for twins are nearly 2 to 4 times higher than those for singleton births [14–16]. A population-based study conducted in the U.S. revealed that the incidence of PTB among twin pregnancies reached 60.32% in 2018, which is 6 to 10 times greater than the rate observed for singleton pregnancies [17]. Li et al. reported that the prevalence of PTB in twin pregnancies was 60.78% based on data from 3835 twin pairs collected from nine hospitals throughout China in 2016 [18]. To our knowledge, there have been no studies examining the relationship between $PM_{2.5}$ and its components and the risk of PTB among twins in China.

This research utilized data from 8458 twin pairs throughout China to assess the relationship between exposure to $PM_{2.5}$ and its components during pregnancy and the risk of PTB. Additionally, we examined the key exposure periods and identified populations that may be particularly vulnerable to the effects of $PM_{2.5}$. Our results could significantly inform policymakers in crafting intervention strategies aimed at mitigating the risk of preterm birth associated with $PM_{2.5}$ air pollution.

2. Methods

2.1. Study Population

This study initially involved 9429 pregnant women who delivered twins across 21 hospitals in mainland China between January 2010 and December 2020 (Figure S1). Birth records and maternal information were collected from the medical system of hospitals. Information for all the participants included maternal characteristics [such as residential address, date of last menstrual, age, parity, type of conception, pregnancy complications (had any one of the following disease: gestational diabetes mellitus, gestational hyperten-

sion, preeclampsia, eclampsia, chronic hypertension with preeclampsia, pregnancy with chronic hypertension, anemia, hypothyroidism, hyperthyroidism, premature rupture of fetal membranes, fetal distress, abruptio placentae, placenta previa, placenta implantation, oligoamnios, and polyhydramnios)] and infants' characteristics (such as sex, birth date, twin zygosity and chorionicity). Next, we excluded the following: missing residential address during the pregnancy (n = 194), information about the last menstrual date or the birth date (n = 748), and infants' sex (n = 26), and exposure missing (n = 3).

Ultimately, 8458 pairs of twins and their mothers were incorporated into the main analyses. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University [ID: 2020(097)].

2.2. Outcome Measurement

Gestational age was determined using the most accurate obstetrical estimate, which included the date of the last menstrual period and ultrasound findings. Preterm birth was classified as a live birth occurring prior to 37 weeks of gestation.

2.3. Exposure Assessment

We obtained data on $PM_{2.5}$ exposure and its composition—specifically NO_3^-, BC, NH_4^+, SO_4^{2-}, and OM—from the Tracking Air Pollution in China (TAP, https://tapdata.org.cn/, accessed on 1 January 2025), which offered daily comprehensive $PM_{2.5}$ and its composition data at a spatial resolution of 10 km × 10 km since the year 2000. Detailed information on the air pollutant assessment model has been described previously [19,20]. In summary, a two-stage machine learning model was employed to estimate $PM_{2.5}$ concentrations by integrating various data sources, including ground-based observations, satellite aerosol optical depth (AOD), and land use information [20]. The out-of-bag cross-validation results for the full-coverage $PM_{2.5}$ predictions showed an R^2 ranging from 0.80 to 0.88 and a root mean squared prediction error (RMSE) between 13.9 and 22.1 $\mu g/m^3$; additionally, for $PM_{2.5}$ composition concentrations, the R^2 varied from 0.67 to 0.80, while the RMSE ranged from 0.93 to 17.14 $\mu g/m^3$ [19,20], suggesting that the model is robust in predicting both $PM_{2.5}$ levels and their compositional constituents.

In this study, we assessed $PM_{2.5}$ and its composition exposure based on each participant's residential address using four exposure windows, that is the early pregnancy (1st to 13th week of pregnancy), the middle pregnancy (14th to 27th week of pregnancy), the late pregnancy (28th week of pregnancy to delivery), and the whole pregnancy (from conception to delivery).

Given that O_3, NO_2, SO_2, and CO were associated with elevated PTB risk [1,21], we incorporated these air pollutants as confounders in our models, respectively. The dataset for the ground maximum daily 8-h average ozone (MDA8 O_3) was acquired from the TAP (https://tapdata.org.cn/, (accessed on 1 January 2025) at a spatial resolution of 10 km by 10 km. The TAP MDA8 O_3 data was derived using a data-fusion algorithm, with five-fold cross-validation employed to assess its performance. The resulting R^2 and RMSE values for MDA8 O_3 were 0.70 and 26 $\mu g/m^3$, respectively [22]. Data on NO_2, CO, and SO_2 were obtained from the China High Air Pollutants [CHAP, https://weijing-rs.github.io/product.html, (accessed on 1 January 2025)] dataset. This dataset employs a combination of satellite remote sensing, extensive ground-based observations, atmospheric reanalysis, emission inventories, and model simulations, leveraging artificial intelligence to account for the spatiotemporal variability of air pollution.

Ambient temperature and relative humidity (RH) dataset at a 0.25° × 0.25° spatial resolution was extracted from the ERA-5 reanalysis, which offers data at a spatial resolution of 0.25° × 0.25° [23]. A previous study has compared daily temperature and

relative humidity from ERA-5 with that from multiple weather stations in China using 10-fold cross-validation, and the R^2 and RMSE were 0.93 and 3.22 °C for temperature, 0.84 and 7.71% for RH, respectively [24], which suggests that ERA-5 data were reliable.

To assess the greenness levels of participants, we utilized the normalized difference vegetation index (NDVI) sourced from the Moderate Resolution Imaging Spectroradiometer (MODIS) through the Google Earth Engine (GEE, https://earthengine.google.com/, accessed on 1 January 2025). This platform offers vegetation index products (MOD13Q1) with a spatial resolution of 250 m by 250 m and a temporal resolution of 16 days. NDVI serves as a measure of the density of green vegetation, with values spanning from −1 to 1. Elevated positive values signify a greater abundance of greenery. From 2010 to 2020, we collected the maximum monthly NDVI data within a 500-m circular buffer based on the residential addresses of participants during their pregnancies.

Identical windows for $PM_{2.5}$ and its composition exposures were selected for other air pollutants, ambient temperature, RH, and NDVI.

2.4. Covariates

We chose the confounders listed below due to their relationships with $PM_{2.5}$ and PTB [2,25,26], as well as the availability of data: (1) mother's characteristics including maternal age, parity (nulliparous or multiparous), complications of pregnancy (yes or no), and mode of delivery (vaginal or cesarean); (2) infant characteristics including sex of the twins (male and female, male and male, or female and female), zygosity chorionicity (monochorionic monoamniotic, monochorionic diamniotic, or dichorionic diamniotic), and birth seasons [Spring (March to May), Summer (June to August), Autumn (September to November), or Winter (December to February)]; and (3) meteorological conditions including ambient temperature and RH.

2.5. Statistical Analysis

The relationships between PTB and prenatal exposure to $PM_{2.5}$ and its components were assessed using generalized linear models (GLM), accounting for all previously mentioned covariates. For an interquartile range (IQR) increment in $PM_{2.5}$ and its composition, the effect estimates were presented as odds ratios (ORs) and 95% CIs for the risk of PTB. Furthermore, to investigate potential nonlinear exposure–response relationships between $PM_{2.5}$, its components, and PTB, we employed natural regression splines with three knots in the model.

Then, we employed the subsequent equation to determine the population attributable fraction (*PAF*) of PTB attributable to $PM_{2.5}$ mass [27]:

$$PAF = \frac{\sum(P_i \times exp(\beta \times \Delta C_i)) - 1}{\sum(P_i \times exp(\beta \times \Delta C_i))}$$

P_i: the percentage of population with exposure to $PM_{2.5}$ concentration i;

β: the estimate coefficient of PTB attributable to $PM_{2.5}$ in the GLM model;

ΔC_i: the difference between $PM_{2.5}$ concentration of each participant and the reference concentration.

According to China's air quality standards, 15 $\mu g/m^3$ was selected as a reference level. This implies that the ΔC_i will equal zero when the $PM_{2.5}$ concentration is at or below this threshold.

To explore the potential effect modifiers, we conducted stratified analyses by type of pregnancy (natural pregnancy or ART), pregnancy complications (yes or no), region (Southern or North), and ambient temperature (<median or ≥median). An interaction term

involving $PM_{2.5}$, its chemical compositions, and a stratified variable was incorporated into the GLM to assess the modifying effect of each stratified variable.

Ultimately, we assessed the robustness of the findings by conducting several sensitivity analyses: (1) we fitted GLM for $PM_{2.5}$ during the whole pregnancy with additional adjustment for MDA8 O_3, NO_2, SO_2, or CO; (2) we additionally excluded participants with gestational hypertension; (3) we additionally excluded participants with gestational diabetes; 4) we additionally excluded participants with birth defect.

All statistical analyses were performed using R software (version 4.3.2). Statistical tests were two-sided, and the significance level was set at $p < 0.05$.

3. Results

3.1. Characteristics of Study Subjects

In this study, a total of 5592 (66.11%) twin pairs of PTB were identified among 8458 live twin births. Of 8458 live twin births, 65.3% were nulliparous, 59.9% were conceived by ART, and 88.8% delivered by cesarean. The mean age [±standard deviation (SD)] of women in the PTB subgroup was 31.1 ± 4.56 years, and the gestational age (±SD) was 35.4 ± 2.56 weeks. Moreover, the proportion of participants living in Southern China in the PTB subgroup (82.2%) was lower than in the subgroup of term birth (85.0%, $p = 0.001$) (Table 1).

Table 1. Summary characteristics of the study population.

Characteristics n (%)/Mean ± SD	Total n = 8458	PTB n = 5592	Term n = 2866	*p* Value [a]
Maternal age (Years)	31.1 ± 4.56	31.1 ± 4.72	31.3 ± 4.25	0.038
Maternal age (Years)				
<30	3075 (36.4)	2094 (37.5)	981 (34.3)	0.004
≥30	5370 (63.6)	3492 (62.5)	1878 (65.7)	
Gestational age (Weeks)	35.4 ± 2.56	34.4 ± 2.55	37.5 ± 0.53	<0.001
Residential area				0.001
Southern	7031 (83.1)	4596 (82.2)	2435 (85.0)	
Northern	1427 (16.9)	996 (17.8)	431 (15.0)	
Residential area				<0.001
Rural	2870 (33.9)	2024 (36.2)	846 (29.5)	
Urban	5588 (66.1)	3568 (63.8)	2020 (70.5)	
Parity				1.000
Nulliparous	5510 (65.3)	3644 (65.2)	1866 (65.3)	
Multiparous	2934 (34.7)	1941 (34.8)	993 (34.7)	
Type of conception				0.001
Natural pregnancy	3372 (40.1)	2297 (41.3)	1075 (37.6)	
Assisted reproduction	5047 (59.9)	3266 (58.7)	1781 (62.4)	
Mode of delivery				<0.001
Vaginal	948 (11.2)	797 (14.3)	151 (5.29)	
Cesarean	7483 (88.8)	4777 (85.7)	2706 (94.7)	
Gestational diabetes				0.449
No	6511 (78.3)	4281 (78.0)	2230 (78.8)	
Yes	1807 (21.7)	1206 (22.0)	601 (21.2)	
Gestational hypertension				<0.001
No	7027 (84.6)	4458 (81.3)	2569 (91.1)	
Yes	1278 (15.4)	1028 (18.7)	250 (8.87)	
Birth season				0.731
Spring	2171 (25.7)	1432 (25.6)	739 (25.8)	
Summer	2281 (27.0)	1510 (27.0)	771 (26.9)	
Autumn	1915 (22.6)	1250 (22.4)	665 (23.2)	
Winter	2091 (24.7)	1400 (25.0)	691 (24.1)	
Sex				<0.001
Male-female	3023 (35.7)	1901 (34.0)	1122 (39.1)	
Male-male	3053 (36.1)	2107 (37.7)	946 (33.0)	
Female-female	2382 (28.2)	1584 (28.3)	798 (27.8)	
Zygosity chorionicity				<0.001
Monochorionic monoamniotic	96 (1.20)	84 (1.61)	12 (0.43)	
Monochorionic diamniotic	1736 (21.7)	1338 (25.7)	398 (14.3)	
Dichorionic diamniotic	6173 (77.1)	3794 (72.7)	2379 (85.3)	

Table 1. *Cont.*

Characteristics n (%)/Mean ± SD	Total n = 8458	PTB n = 5592	Term n = 2866	*p* Value [a]
$PM_{2.5}$ (μg/m^3)	37.5 (12.8)	38.2 (13.1)	36.0 (11.8)	<0.001
NH_4^+ (μg/m^3)	4.52 (2.04)	4.63 (2.07)	4.30 (1.96)	<0.001
SO_4^{2-} (μg/m^3)	7.11 (2.44)	7.25 (2.55)	6.82 (2.19)	<0.001
NO_3^- (μg/m^3)	6.47 (3.31)	6.60 (3.36)	6.20 (3.18)	<0.001
BC (μg/m^3)	2.05 (0.69)	2.08 (0.73)	1.97 (0.61)	<0.001
OM (μg/m^3)	9.92 (3.04)	10.0 (3.19)	9.69 (2.72)	<0.001

Note: SD, standard deviation; PTB, preterm birth; $PM_{2.5}$, fine particulate matter; NH_4^+, ammonium; SO_4^{2-}, sulfate; NO_3^-, nitrate; BC, black carbon; OM, organic matter. [a] Chi-square test was applied to compare the differences in categorical variables between PTB and term groups; *t*-test was applied to compare the differences in continuous variables between PTB and term groups.

During the entire pregnancy, the average levels of $PM_{2.5}$, NH_4^+, SO_4^{2-}, NO_3^-, BC, and OM were 37.50 (SD = 12.76) μg/m^3, 4.52 (SD = 2.04) μg/m^3, 7.11 (SD = 2.44) μg/m^3, 6.47 (SD = 3.31) μg/m^3, 2.05 (SD = 0.69) μg/m^3, and 9.92 (SD = 3.04) μg/m^3, respectively. The trimester-specific exposure data is shown in Table S1.

Strong correlations were identified between $PM_{2.5}$ mass and the five chemical compositions (r = 0.88–0.96, all $p < 0.001$), whereas weak to moderate correlations were observed between $PM_{2.5}$ mass and other air pollutants, TM and RH (r = −0.04–0.46, all $p < 0.001$) (Table S2).

3.2. Associations of Prenatal $PM_{2.5}$ and Its Composition Exposures with PTB

We first investigated the nonlinear exposure–response relationship between $PM_{2.5}$, its chemical compositions, and the risk of PTB. We observed a linear relationship for $PM_{2.5}$ and SO_4^{2-} during the entire pregnancy ($p_{\text{nonlinear}}$ = 0.647 and $p_{\text{nonlinear}}$ = 0.747), and nonlinear associations for SO_4^{2-}, NO_3^-, BC, and OM (all $p_{\text{nonlinear}} < 0.05$) during the whole pregnancy (Figure 1). Figures S2–S4 illustrate the nonlinear relationship between $PM_{2.5}$ and its components concerning PTB across each trimester.

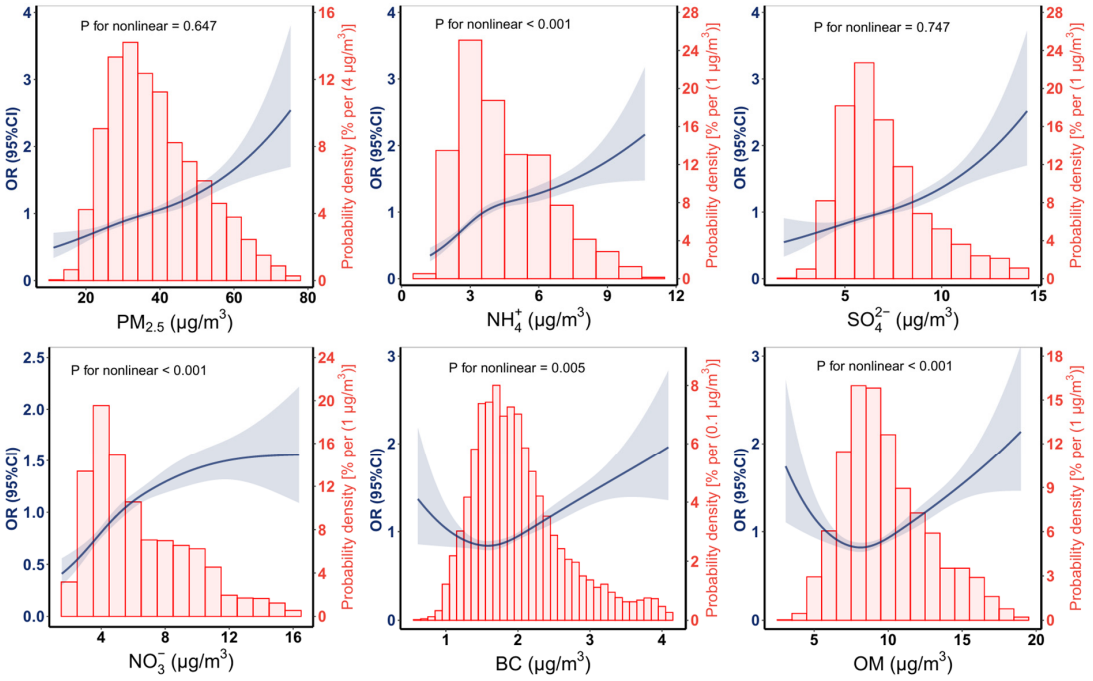

Figure 1. Exposure–response relationship curve for $PM_{2.5}$ and its constituent exposure during the entire pregnancy and risk of preterm birth. $PM_{2.5}$, fine particulate matter; NH_4^+, ammonium; SO_4^{2-}, sulfate; NO_3^-, nitrate; BC, black carbon; OM, organic matter. Models were adjusted for maternal age, parity, gestational hypertension, gestational diabetes, twin zygosity and chorionicity, seasons of delivery, sex of twin fetuses, ambient temperature, and relative humidity.

The associations of $PM_{2.5}$ and chemical compositions with PTB are shown in Table 2. The ORs (95% CI) for an IQR increment in $PM_{2.5}$ (17.57 μg/m^3), NH_4^+ (2.98 μg/m^3), SO_4^{2-} (2.81 μg/m^3), NO_3^- (4.55 μg/m^3), BC (0.78 μg/m^3), and OM (3.84 μg/m^3) during the entire pregnancy were 1.46 (1.34–1.59), 1.54 (1.39–1.70), 1.34 (1.25–1.44), 1.44 (1.30–1.59), 1.28 (1.20–1.37), and 1.28 (1.18–1.38), respectively.

Table 2. Associations of prenatal $PM_{2.5}$ and its constituent exposures with preterm birth.

Pollutants	Entire Pregnancy		Trimester 1		Trimester 2		Trimester 3	
	IQR (μg/m^3)	OR (95% CI)	IQR (μg/m^3)	OR (95% CI)	IQR (μg/m^3)	OR (95% CI)	IQR (μg/m^3)	OR (95% CI)
$PM_{2.5}$	17.57	1.46 (1.34, 1.59)	20.58	1.33 (1.22, 1.46)	19.78	1.26 (1.16, 1.37)	20.48	1.40 (1.28, 1.52)
NH_4^+	2.98	1.54 (1.39, 1.70)	3.17	1.29 (1.18, 1.41)	3.18	1.24 (1.13, 1.35)	3.15	1.37 (1.26, 1.49)
SO_4^{2-}	2.81	1.34 (1.25, 1.44)	3.19	1.24 (1.16, 1.32)	3.14	1.20 (1.13, 1.29)	3.32	1.34 (1.25, 1.43)
NO_3^-	4.55	1.44 (1.30, 1.59)	5.25	1.23 (1.13, 1.35)	5.27	1.19 (1.09, 1.31)	5.09	1.34 (1.23, 1.47)
BC	0.78	1.28 (1.20, 1.37)	0.94	1.24 (1.16, 1.32)	0.93	1.17 (1.09, 1.25)	0.99	1.25 (1.17, 1.34)
OM	3.84	1.28 (1.18, 1.38)	4.81	1.20 (1.11, 1.30)	4.69	1.14 (1.05, 1.23)	5.03	1.25 (1.16, 1.35)

Abbreviations: IQR, interquartile range; $PM_{2.5}$, fine particulate matter; n, the number of preterm birth in each subgroup; N, the total number of participants in each subgroup; OR, odds ratio; CI, confident interval; TM, ambient temperature; NH_4^+, ammonium; SO_4^{2-}, sulfate; NO_3^-, nitrate; BC, black carbon; OM, organic matter. The median TM is 20.5 °C. Models adjusted for maternal age, parity, gestational hypertension, gestational diabetes, twin zygosity and chorionicity, seasons of delivery, sex of twin fetuses, and relative humidity.

In trimester-specific analyses, the OR (95% CI) for an IQR increase in $PM_{2.5}$ concentration in the first (20.58 μg/m^3), second (19.78 μg/m^3), and third (20.48 μg/m^3) trimester of pregnancy were 1.33 (1.22–1.46), 1.26 (1.16–1.37), and 1.40 (1.28–1.52), respectively (Table 2). We observed similar associations of chemical compositions with PTB risk during the first, second, and third trimester (all $p < 0.05$) (Table 2).

Stratified analyses showed slightly stronger associations between $PM_{2.5}$ and PTB in participants living in Northern China (OR = 1.43, 95% CI: 1.20, 1.73) than in Southern China (OR = 1.36, 95% CI: 1.24, 1.49, $p_{\text{interaction}} = 0.465$), in warmer regions (OR = 1.39, 95% CI: 1.26, 1.54) than in colder regions (OR = 1.24, 95% CI: 1.10, 1.40, $p_{\text{interaction}} = 0.124$), and in less greenness areas (OR = 1.69, 95% CI: 1.48, 1.94) than in more greenness areas (OR = 1.28, 95% CI: 1.13, 1.45, $p_{\text{interaction}} < 0.001$) during the whole pregnancy. Similar associations of $PM_{2.5}$ compositions with PTB were observed in each subgroup (Figure 2, Table S3).

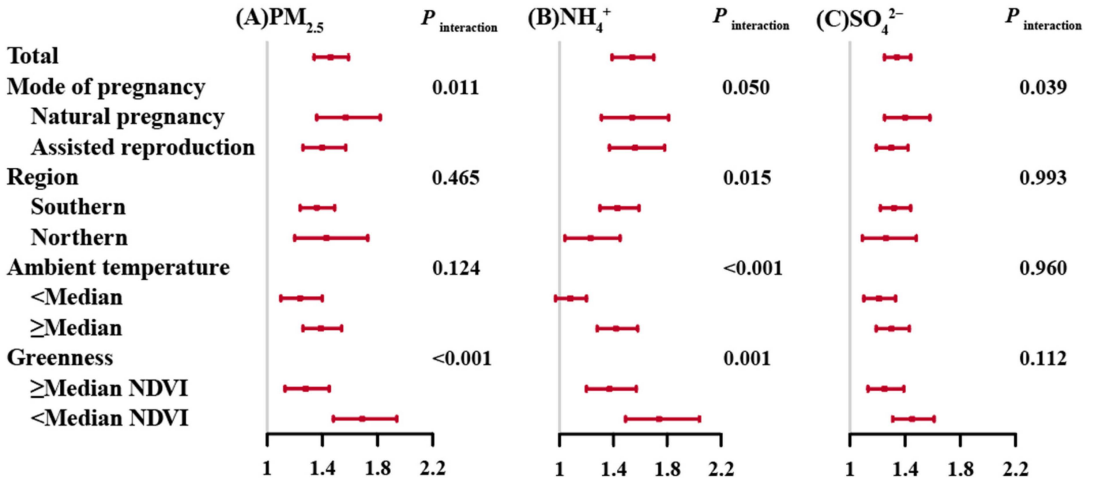

Figure 2. *Cont.*

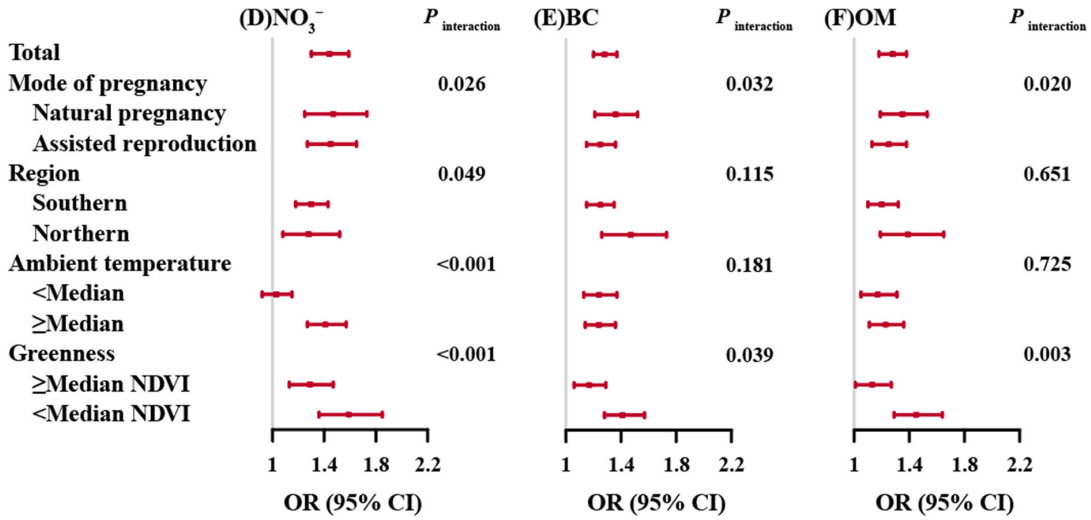

Figure 2. Associations of maternal $PM_{2.5}$ and its components exposure with preterm birth in each subgroup. Abbreviations: $PM_{2.5}$, fine particulate matter; NH_4^+, ammonium; SO_4^{2-}, sulfate; NO_3^-, nitrate; BC, black carbon; OM, organic matter; NDVI, normalized difference vegetation index; OR, odds ratio; CI, confidence interval. The median ambient temperature is 20.5 °C. Models adjusted for maternal age, parity, gestational hypertension, gestational diabetes, twin zygosity and chorionicity, seasons of delivery, sex of twin fetuses, ambient temperature, and relative humidity (except for the stratified variable).

3.3. PAF of PTB Attributable to Prenatal Exposure to $PM_{2.5}$

The *PAF* of PTB was 40.75% (95% CI: 32.5%, 48.26%) in the total population. Subgroup analyses showed higher *PAF*s of SGA risk attributable to $PM_{2.5}$ in participants living in northern China (56.69%, 95% CI, 32.69%–73.22%), in warmer regions (41.51%, 95% CI, 30.45%–51.28%), and in higher residential greenness areas (52.62%, 95% CI, 41.71%–61.92%), (Figure 3 and Table S4).

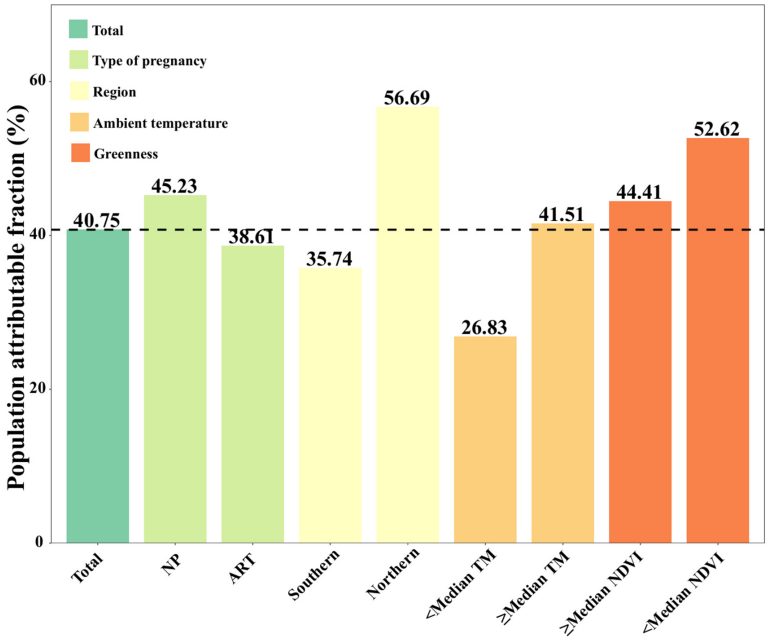

Figure 3. The population-attributable fraction of preterm birth for maternal exposure to $PM_{2.5}$. Abbreviations: $PM_{2.5}$, fine particulate matter; NP, natural pregnancy; ART, assisted reproductive technology; TM, ambient temperature; NDVI, normalized difference vegetation index. The median TM is 20.5 °C.

3.4. Sensitivity Analyses

The sensitivity analyses indicated robustness of our results against additional adjustment for other air pollutants, and excluded participants with gestational hypertension, gestational diabetes, or birth defects (Table S5).

4. Discussion

Utilizing a nationwide sample of twins in China, we discovered that exposure to higher levels of prenatal $PM_{2.5}$ and its components significantly increased the risk of PTB. This risk was higher during the late pregnancy and among participants living in warm regions, and with higher residential greenness. These findings could serve as a strong foundation for developing interventions aimed at reducing PTB associated with $PM_{2.5}$ exposure.

Previous research has investigated the impact of prenatal exposure to $PM_{2.5}$ on the risk of preterm birth in China and other nations; however, the findings have been inconsistent. A study conducted in Shanghai, China, involving 3692 singleton live births, revealed that maternal exposure to $PM_{2.5}$ heightened the risk of preterm birth [28]. Cai et al. identified an increased risk of PTB linked to maternal exposure to $PM_{2.5}$, analyzing data from 77,879 infant–mother pairs across 25 provinces in mainland China [29]. A study conducted in London revealed a positive correlation between maternal exposure to $PM_{2.5}$ and the risk of PTB based on an analysis of 578,382 live birth records [30]. Consistent with these findings, our analysis of 8458 twin pairs from China indicated an increased risk of PTB associated with increased $PM_{2.5}$ exposure. To date, no study has examined the risk of PTB associated with maternal exposure to $PM_{2.5}$ using twin data in China. Our results show that $PM_{2.5}$ exposure could induce PTB. Therefore, controlling $PM_{2.5}$ levels may help to reduce the occurrence of PTB, improve children's health, and alleviate the burden on families.

The biological processes linking $PM_{2.5}$ to PTB remain inadequately understood; however, several hypotheses have been suggested. First, $PM_{2.5}$ is linked to systemic oxidative stress [31], which negatively impacts the embryo during its initial stages of development [32]. Second, $PM_{2.5}$ can accumulate in the lungs and subsequently enter the bloodstream, potentially inducing systemic inflammation or crossing the placenta via simple diffusion [33]. The direct detrimental impact of $PM_{2.5}$ on placental inflammation could lead to changes in placental vascular function [34,35], ultimately contributing to PTB. Third, $PM_{2.5}$ may impact endothelial functions, and such damage could subsequently reduce blood flow to the placenta, disrupt trans-placental oxygenation and nutrient transport, resulting in PTB [36,37].

Fetal growth during pregnancy varies at each stage; identifying the sensitive exposure window of $PM_{2.5}$ is of great significance to take measures to reduce the risk of PTB. The findings from the current study indicate that pregnant women exhibit sensitivity to $PM_{2.5}$ exposure during all trimesters of pregnancy. Consistent with our findings, a recent study by Sally et al. revealed that increased $PM_{2.5}$ exposure during any trimester is associated with a greater risk of PTB based on data from 5,155,026 births in California [2]. The placenta begins to develop, and organogenesis takes place in early pregnancy. Research indicates that $PM_{2.5}$ exposure during this critical period may elevate the risk of hypertensive disorders in pregnancy by disrupting placental function, which can result in preterm birth [38]. Research has demonstrated that during mid-pregnancy, as gestation advances, blood flow between the fetus and placenta progressively increases to satisfy the growing demand for oxygen and nutrients by the fetus [39]. Moreover, $PM_{2.5}$ exposure during late pregnancy can trigger specific cytokines associated with inflammation, potentially leading to preterm birth [40,41]. And fetal weight velocity reaches its peak in late pregnancy (around 35th gestation week) [42], so exposure to $PM_{2.5}$ during this period may impact

fetal growth and contribute to developmental abnormalities, ultimately increasing the risk of PTB. Understanding the critical periods of exposure can greatly aid pregnant women in implementing strategies to reduce the risk of PTB.

The detrimental impacts of $PM_{2.5}$ can differ based on its chemical composition. To date, research on the link between prenatal exposure to specific $PM_{2.5}$ compositions and PTB remains scarce, particularly concerning twin pregnancies. To the best of our knowledge, this is the inaugural study examining the influence of $PM_{2.5}$ and its chemical compositions on the risk of PTB in twins, utilizing data from China. In our results, we found that the risk of PTB is elevated with higher exposure to NH_4^+, SO_4^{2-}, NO_3^-, BC, and OM. The strong association of PTB with NH_4^+, SO_4^{2-}, NO_3^-, and BC, and PTB with NH_4^+ and NO_3^- was confirmed by studies from China and California, respectively [29,43]. However, one study from Atlanta found no association of NH_4^+ and NO_3^- with PTB based on 476,489 birth data [44]. The varying impacts of $PM_{2.5}$ chemical compositions on human health in various studies may be due to the population characteristics, the levels of specific chemical composition, and the methodologies used for assessing exposure.

The five chemical compositions of $PM_{2.5}$—NH_4^+, SO_4^{2-}, NO_3^-, BC, and OM—primarily originate from anthropogenic sources. NH_4^+, SO_4^{2-}, and NO_3^- primarily originate from industrial coal combustion, emissions from fuel-powered vehicles, and operations of coal-fired power plants [45,46]. BC is mainly linked to primary sources such as exhaust from vehicles, burning of biomass, and the combustion of fossil fuels [47,48]. OM can be traced back to the burning of biomass, emissions of dust, and exhaust from vehicles [49]. Evidence indicates that NH_4^+, SO_4^{2-}, and NO_3^- may trigger systemic inflammation [50,51], potentially influencing placental blood flow and hindering fetal development, which can lead to negative birth outcomes [51,52]. BC has the potential to cross to the fetal side of the placenta, possibly impacting fetal growth through inflammation induction [53]. OM can reduce the effectiveness of antioxidant enzymes, leading to PTB [54].

In addition, we noted that pregnant women residing in warmer areas are more vulnerable to $PM_{2.5}$ exposure. The possible mechanism is that heat exposure may enhance sweating, increase skin blood flow, and elevate minute ventilation, resulting in greater absorption of air pollutants [55]. Furthermore, both heat stress and $PM_{2.5}$ can induce systemic inflammation and oxidative stress, which may explain why the effects of $PM_{2.5}$ are more pronounced at elevated temperatures [56,57]. In addition, our findings indicate that greater residential greenness can mitigate the negative effects of $PM_{2.5}$ on PTB. Two underlying mechanisms that may explain the attenuating impact on PTB of greenness. First, vegetation can enhance air quality by trapping air pollutants on surfaces like leaves and bark [58]. Second, having residential greenness may promote physical activity, which is associated with favorable birth outcomes [59]. Further research is necessary to validate our findings and enhance understanding of the underlying mechanisms, enabling protective measures for vulnerable populations.

Our results indicated that the *PAF* of PTB caused by prenatal exposure to $PM_{2.5}$ was 40.75%. The total annual number of twin pregnancies in China remains unknown. However, based on a statistic of 64 medical units in different regions and at different levels across China in 2019, the rate of twin pregnancy is 3.69% [60]. In 2023, approximately 9.02 million infants were born [1], with an estimated 330,000 twin pregnancies. Based on the latest statistics from 48 medical facilities across various regions and levels in 2019, the PTB rate in twin pregnancies is 58.71% [60]. Consequently, the estimated number of PTB in twin pregnancies is 193,743, with approximately 78,950 potentially linked to prenatal exposure to $PM_{2.5}$.

With the continuous development of ART, the rate of twin pregnancy has markedly risen in countries worldwide [61]. According to data from 556,298 newborns across

64 medical institutions in China, the incidence of twin pregnancies in the Chinese population is 3.69%, indicating an upward trend [60]. In twin pregnancies, the incidence of PTB is as high as 60%, 6 to 10 times greater than in singleton pregnancies [17]. Twin pregnancies encounter the same complications as singleton pregnancies, but at elevated rates, especially regarding PTB. Therefore, identifying potential modifiable risk factors for PTB is essential for enhancing child health outcomes. In this study, we identified that $PM_{2.5}$ exposure can increase the risk of PTB in twin pregnancies, providing evidence for policymakers to implement measures aimed at improving air quality.

This study has several strengths. First, this study is the first to establish the association between $PM_{2.5}$ and its chemical components and an elevated PTB risk in twin pregnancies in China. Second, the large sample size of this study allows for stratified analysis to identify sensitive populations so that more targeted measures can be taken to reduce the rate of PTB.

This study also possesses some limitations. First, exposure levels in this study were determined based on the residential addresses of pregnant women during their pregnancies, without considering their living conditions, which may introduce bias in exposure assessment. Second, we only accounted for certain confounders, such as maternal age and the sex of the twins. Other relevant characteristics, like the occupation of pregnant women and folic acid supplementation, could also influence the association but were not included due to a lack of available data. Third, PTB may be related to genetic factors, but this study did not consider the effect of genetic factors in the association between air pollutants and PTB, so caution should be exercised in interpreting the results. Finally, in areas with severe air pollution, $PM_{2.5}$ exposure in early pregnancy may be more likely to cause miscarriage, malformations, and stillbirths [41]. As a result, we cannot estimate the effects of $PM_{2.5}$ on PTB risk among these people, which would weaken the association between $PM_{2.5}$ and PTB.

5. Conclusions

Our findings provide evidence of a higher risk of PTB related to prenatal exposure to $PM_{2.5}$, and the associations are significant at any trimester of pregnancy. In addition, participants living in warmer regions and lower levels of residential greenness may be more sensitive to $PM_{2.5}$. Our findings may be of great significance in setting up targeted policies to reduce the harmful effects of air pollution on pregnant women and their fetuses.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/greenhealth1020011/s1. Table S1. Exposure Characteristics of $PM_{2.5}$ and its components (Mean ± SD). Table S2. Correlation coefficients for ambient pollutants, ambient temperature, and relative humidity during the entire pregnancy. Table S3. Associations of an IQR increase in $PM_{2.5}$ and its component exposures with preterm birth in each subgroup. Table S4. The *PAF* of preterm birth for maternal exposure to $PM_{2.5}$. Table S5. Associations of an IQR increment in $PM_{2.5}$ during the entire pregnancy with the risk of preterm birth. Figure S1. Hospital distribution of 21 Grade-A tertiary hospitals in China. Figure S2. Exposure-response relationship curve for air pollutants exposure during the trimester 1 and the risk of preterm birth. Figure S3. Exposure-response relationship curve for air pollutants exposure during the trimester 2 and the risk of preterm birth. Figure S4. Exposure-response relationship curve for air pollutants exposure during the trimester 3 and the risk of preterm birth.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Third Affiliated Hospital of Guangzhou Medical University [ID: 2020(097)] on 23 October 2020.

Informed Consent Statement: Patient consent was waived due to our research is a retrospective study, only the consent of the ethics committee, without the informed consent of the participants.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author(s).

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