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Maternal ambient air pollution exposure with spatial-temporal variations and preterm birth risk assessment during 2013–2017 in Zhejiang Province, China

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ABSTRACT

Preterm birth (PTB) can give rise to significant neonatal morbidity and mortality, as well as children's long-term health defects. Many studies have illustrated the associations between ambient air pollution exposure during gestational periods and PTB risks, but most of them only focused on one single air pollutant, such as $PM_{2.5}$. In this population-based environmental-epidemiology study, we recruited 6275 pregnant mothers in Zhejiang Province, China, and evaluated their gestational exposures to various air pollutants during 2013–2017. Time-to-event logistic regressions were performed to estimate risk associations after adjusting all confounders, and Quasi-AQI model and PCA-GLM analysis were applied to resolve the collinearity issues in multi-pollutant regression models. It was found that gestational exposure to ambient air pollutants was significantly associated with the occurrence of PTB, and SO_2 was the largest contributor with a proportion of 29.4%. Three new variables, *prime factor* (a combination of $PM_{2.5}$, PM_{10}, SO_2, and NO_2), *carbon factor* (CO), and *ozone factor* (O_3), were generated by PCA integration, contributing 63.4%, 17.1%, and 19.5% to PTB risks, respectively. The first and third trimester was the most crucial exposure window, suggesting the pregnant mothers better to avoid severe air pollution exposures during these sensitive periods.

1. Introduction

The ambient air pollution has been getting increasingly prominent in recent years due to the rapid industrialization and urbanization globally (WHO, 2018), accounting for various types of non-communicable diseases and even lung cancer, after long-term or short-term exposure, which have been confirmed by epidemiological studies (Brook et al., 2010; Hamra et al., 2014; Zhu et al., 2019). Particulate matters (PMs) are mostly originated from fossil fuel-based industrial activities and wide use of vehicles in developed countries (Gower and McColl, 2005), and emitted from incomplete combustion of rudimentary solid fuels for electricity generation, daily cooking and heating in developing countries (Huang et al., 2014; Shen et al., 2019). The fine PMs especially, defined as aerodynamic diameter lower than 2.5 μm ($PM_{2.5}$), can penetrate more deeply into the respiratory tract, reach the alveolar capillaries, and permeate into the blood circulation system, leading to series of chronic symptoms, or even premature death (Almeida-Silva et al., 2018; Balakrishnan et al., 2004; Lin et al., 2008; Rajagopalan and Brook, 2012; Simkhovich et al., 2008; Smith et al., 2011). Anthropogenic activities are also responsible for emissions of

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Abbreviations: PTB, preterm birth; AQI, air quality index; PCA, principal component analysis; GLM, generalised linear model; PM, particulate matter; HBP, high blood pressure; OR, odds ratio; BMI, body mass index; LUR, land use regression; SD, standard deviation; IQR, inter-quartile range; CI, confidence interval; VOC, volatile organic compound; LOAEL, lowest observed adverse effect level

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other criteria air pollutants, such as SO_2, NO_2, CO and O_3 (Marc et al., 2016; Sun et al., 2016; Yang et al., 2013; Zhong et al., 2017), which can also lead to numbers of diseases (DeVries et al., 2017; Ghozikali et al., 2015).

Reproductive health may be closely associated with ambient air pollution exposures, as pregnant mothers and new-borns are both vulnerable populations (Latzin et al., 2009; Song et al., 2019; Srám et al., 2005; Wang et al., 2015). Premature delivery is one of the typical health burdens that can be attributable to maternal air pollution exposure during pregnancy, as has been epidemiologically manifested in several studies (Bobak, 2000; Brook et al., 2010; Lee et al., 2003, 2013; Maisonet et al., 2001; Ritz and Yu, 1999; Ritz et al., 2000; Wang et al., 2018a, 2018b; Yu et al., 2019). Air pollution exposure associated preterm birth (PTB) risks are attracting ever-growing attention since PTB can result in higher risk of morbidity, growth restriction or even mortality of the infant (Fleischer et al., 2014), and some of the adverse health effects can last until adulthood (Longo et al., 2013; Rogers and Velten, 2011). However, most of such environmental-epidemiological studies on mother-child birth pairs were conducted in developed countries, and only a few studies were performed in China, with large proportion in northern China and megacities, where air pollution concentrations were frequently reported to be high. Zhejiang Province, located on the southeast coast of China and subordinate to the Yangtze River Delta Region, is of different air pollution patterns from northern China: the pollution levels of O_3 and NO_x in Zhejiang province were reported to be more prominent compared to $PM_{2.5}$ issues in northern China (Chen et al., 2018), but no studies on air pollution exposure induced PTB for Zhejiang population were conducted according to the authors' knowledge. In addition, to date, most of the published relevant studies explored the exposure risks of only one single air pollutant.

In this context, our study will explore the association between PTB risks and maternal exposures to ambient air $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 from the recruited 6275 effective mother-child pairs in Zhejiang Province during 2013–2017. At the meantime, exposure risk contributions from six studied pollutants during different gestational trimesters will all be evaluated, together with consideration of all involved covariates. In a word, our research will fill in the literature gap, provide evidence-based practical suggestions on reducing the PTB risks as a result of air pollutants exposures, and also suggest feasible methods for more credible assessment on risk associations of multi-pollutant exposures.

2. Methodology

2.1. Participants and health outcome

It was a prospective birth cohort started on January 1, 2013, aiming at recording the health conditions of mother-child pairs on a rolling basis. The cohort consisted of mothers from different regions across Zhejiang Province, China. Setting June 30, 2017, as the observation end of this study, 6789 participants were preliminarily recruited with written consents after elimination of twins, triplets, quadruplets, and stillbirths. The primary health outcome for analysis was the gestational age scaled to days, and PTB was defined as gestational age less than 37 weeks (252 days).

The residential address, physical features including height, weight, gestational hypertension (maternal high blood pressure, HBP), and sociological characters like age and occupation, of the enrolled mothers, were collected from official hospital registration records and an additional questionnaire during their parturition hospitalization. The accurate dates for pregnant mothers to start conception were defined using ultrasound techniques.

Incompletion and errors in documentation could jeopardise the integrity of the database and impair the statistical inferences, so that we cleaned and censored the records following previously published criteria (Bell et al., 2007; Di et al., 2016; Ritz et al., 2007), which could also ensure the consistency of our results with literature. Totally 157 (2.3%) participants were excluded due to missing, or incorrect recording of conceiving or delivery dates; 256 (3.8%) were deleted owing to faultiness in physiological and sociological features such as maternal age, height, weight, blood pressure, gravidity and parity times; 13 (0.2%) were dropped as these participants experienced movement in residence, and 66 (1.0%) eliminated because of lacking address location information. Thus, 6297 (92.7%) participants were kept for air pollution exposure estimation (Fig. A.1).

2.2. Concentration and exposure of air pollutants

The primary exposures for the pregnant mothers in this study were their gestational exposures to six ambient air pollutants: $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3. A total of 47 ground-based monitoring stations were involved in this study, recording the 24-h average concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO, and 8-h maximum moving average of O_3, with synchronized hybrid ambient real-time particulate monitor (Model 5030 SHARP monitor, ThermoFisher Scientific Inc., USA). The addresses of the participants and the ambient air monitoring stations were all mapped in Fig. A.2. Exposure concentrations to the ambient air pollutants were identified onto every participant with specific addresses using minimum Euclidean distance matching to the nearest ground-based air quality monitoring stations (the reason is stated in Supplementary Materials). The average distance between the residential locations and their corresponding nearest stations was 5.0 ± 15.9 km, with the largest distance of 75.9 km. Exposure windows by month, trimester, and whole gestational periods were all calculated for assessment of PTB risks. Due to the data unavailability of the air pollution monitoring stations in some specific days, 22 (0.3%) participants were excluded as their gestational periods covered these days, so that 6,275 (92.4%) participants were finally included into analyses (Fig. A.1).

2.3. Statistical analysis

Time-to-event regression models were performed to estimate the effects of time-varying gestational exposures to six ambient air pollutants on the occurrence of PTB in terms of odds ratio (OR) (Chang et al., 2011; Chang et al., 2015). In concentration-response relationship estimation, the pollution exposure concentrations were modeled as continuous variables, and a hybrid approach integrating restricted cubic spline model and logistic-shaped curve-fitting regression was applied, to extrapolate the uncovered exposure concentrations, as well as ensure the curve to follow a monotonically increasing pattern. In order to address confounding effects, all collected covariates that were correlated with both the air pollution exposures and abnormal delivery but not in the causal pathway between the exposure and health outcome were involved into consideration. These covariates included age, height, weight, body mass index (BMI), occupation, gestational hypertension (occur or not), and gender of the neonates.

To resolve the mutual interference between the exposure concentrations of different air pollutants when assessing the PTB occurrence risks, quasi-AQI (air quality index) model and PCA-GLM (principal component analysis - generalized linear model) approach were innovatively applied in this study. The principle of quasi-AQI approach followed the definition of AQI which would select the highest individual AQI value of all six studied air pollutants to integrate the multiple concentrations into a single index, but based on the exposure concentrations instead of the environmental concentrations. The PCA-GLM approach would first linearly re-arrange the original variables into fewer new integrated variables (named as principal components) which statistically were not correlated with each other, then evaluate the risk association between PTB occurrences and the newly generated components so as to avoid the collinearity issues (Sun et al., 2017). Spatial auto-correlations of the PTB risks and air pollution concentrations were quantified by semivariograms, and the explanation of spatial dependences were performed by land use regressions (LUR).

All statistical regression analyses were accomplished by Stata 14.2 (Stata Corp, College Station, TX, USA). The spatial statistics and geographical mapping were achieved in R *v*3.4.0 (R Core Team, Vienna, Austria) and ArcMap 10.4 (ESRI, Inc., Redlands, CA, USA). All statistical inferences were completed by 2-sided tests, defining p-value < 0.05 as significant.

3. Results and discussions

3.1. Participant profiles

A total number of 6275 pregnant mothers were followed during 2013–2017 with their basic physiological and sociological features recorded. The average age with standard deviation (SD) when they gave birth was 29.4 ± 3.6, ranging from 22 to 39 (median: 29, interquartile range (IQR): 27–32), and BMI was 25.8 ± 2.8, varying from 19.1 to 33.2 (median: 25.7, IQR: 24.0–27.5). Among all the participants, 53.9% were at their first time for pregnancy, and 76.5% were their first delivery, which was comparatively lower than studies conducted in previous years of China (Qian et al., 2016), reflecting the fact that there were a growing number of mothers starting to conceive more than one child under the "two-child" policy propagated by China's State Council in 2015 (partially launched in 2013). There were 2.45% (95% confidence interval (CI): 2.06–2.81%) suffering from gestational hypertension, and the PTB group was of a higher rate of gestational hypertension. The full-term birth group were of higher BMI but lower in gravidity and parity times.

Within the range of our current study, 1578 (25.1%) mothers started their gestation in 2013, 2305 (36.7%) in 2014, 1486 (23.7%) in 2015, 666 (10.6%) in 2016, and 239 (3.8%) in 2017. Across the 5 years within this research, 1734 (27.6%) started to conceive in spring (March to May), 1566 (25.0%) in summer (June to August), 1218 (19.4%) in autumn (September to November), and 1757 (28.0%) in winter (December to February). More detailed summary of the characteristics of the enrolled participants can be found in Table A.1.

The gestational days and weeks of all the involved participants were 272 ± 12.6 and 38.7 ± 1.82 weeks, respectively, with 372 PTB cases in total. Generally, the prevalence of PTB was 5.9% (95% CI: 5.4–6.5%), with the lowest in 2017 (4.9%, 95% CI: 3.5–6.8%) and the highest in 2016 (6.7%, 95% CI: 5.4–8.2%), but no statistical increasing trend was observed across years (p-*trend* = 0.72). However, significant discrepancies across delivery seasons were manifested ($p < 0.001$), with summer the highest (7.7%, 95% CI: 6.5–9.0%) and winter the lowest (4.6%, 95% CI: 3.7–5.7%).

Geographically, the occurrence risks of premature delivery were generally higher in northern than in southern Zhejiang (Fig. 1), with the highest risks aggregated in Shaoxing, Jinhua, and northeast district of Hangzhou, and the lowest risks concentrated in Taizhou and Lishui. In comparison with other published relevant studies in China, Zhejiang was of relatively higher PTB prevalence (5.9%): Wuhan (Hubei Province) reported 4.5% occurrences from 2011 to 2013 (Qian et al., 2016); Shanghai 4.1% during 2011–2014 (Xiao et al., 2018); 4.4% of nine cities in Guangdong Province from 2014 to 2017 (Liang et al., 2019). In a nutshell, more attention should be paid to premature deliveries, as well as maternal health of the pregnant in Zhejiang, as various health issues that might accompany with the preterm birthed neonates for years could induce family and social burdens in the long run.

3.2. Contamination levels and personal exposures

The temporal trends of the average concentrations of the six pollutants from the 47 sites in Zhejiang Province during 2013–2017 were revealed, with annual and seasonal average concentrations in Table A.2 and Fig. A.3. The overall average concentrations of $PM_{2.5}$, SO_2, NO_2, CO, and O_3 were 45.0 ± 27.1, 15.2 ± 11.2, 37.3 ± 19.9, 941.3 ± 723.0, and 97.8 ± 47.2 $\mu g/m^3$, respectively. According to the national ambient air quality standards, $PM_{2.5}$ and O_3 were still the prime pollutants that need to be handled, as 12.0% of the recording days of ambient air $PM_{2.5}$ and 10.5% of O_3 concentrations across the five studied years exceeded the national suggested safety line (75 $\mu g/m^3$ for $PM_{2.5}$ and 160 $\mu g/m^3$ for O_3) (MEP, 2012). However, the air conditions in Zhejiang Province generally speaking were quite satisfactory according to the national guideline, as nearly all PM_{10} (95.6%), SO_2 (99.9%), NO_2 (96.7%) and CO (99.9%) ambient air concentration records were below the hazardous levels (PM_{10}: 150 $\mu g/m^3$, SO_2: 150 $\mu g/m^3$, NO_2: 80 $\mu g/m^3$, CO: 4 mg/m^3). Although the number of substandard days was low on the whole, the concentrations were still so high in some certain days that the highest concentrations could even reach several folds of the limits, as $PM_{2.5}$ 4.93-fold, PM_{10} 2.47-fold, SO_2 2.93-fold, NO_2 1.76-fold, CO 1.53-fold, and O_3 1.88-fold.

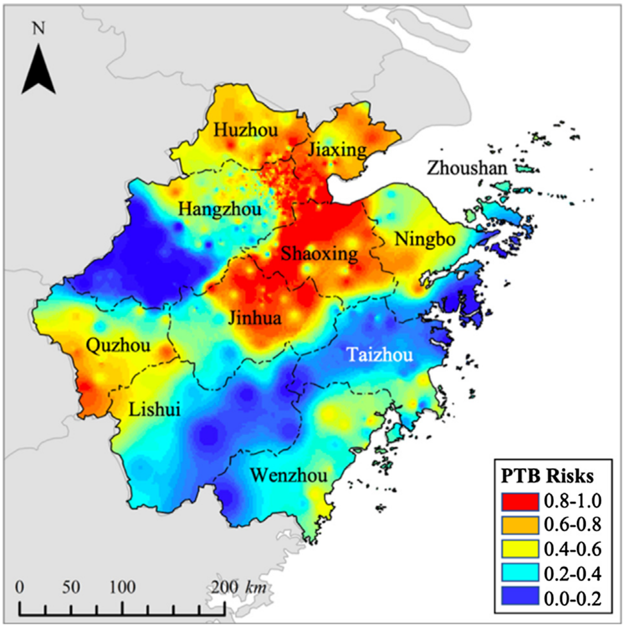

Fig. 1. Geographical risk distributions of preterm birth (PTB) in Zhejiang Province during 2013–2017. The geographical PTB risks were defined as spatial intensity ratios of PTB occurrences, referring to the spatial density of PTB cases compared to the overall density of studied participants, accomplished by kernel estimation with 0.25 km bandwidth. Hot colors represented higher intensities, and cooler colors indicated lower risks, as equally stratified in quintile. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Large variations were found between the 12 months. Setting December as a reference, the geographically averaged concentrations of $PM_{2.5}$, PM_{10}, SO_2 and NO_2 in most of the other months were significantly lower, particularly in July and August, but except $PM_{2.5}$ and PM_{10} in January and SO_2 in January and November. O_3 concentrations were relatively higher from April to October, but no significant monthly variations were observed for CO ($p > 0.17$). More detailed comparisons were summarized in Table A.3. In accordance with previous studies, the ambient air O_3 concentrations were relatively higher in summer, due to the increasing emission of O_3 precursors, the volatile organic compounds (VOCs) for an instance (Sun et al., 2016), and the better condition for O_3 formation (Meleux et al., 2007). Meanwhile, the $PM_{2.5}$, PM_{10}, SO_2, and NO_2 were higher in winter owing to the elevated emission anthropogenic activities, like heating as an example and the relatively worse diffusion condition (Chen et al., 2018; Huang et al., 2014; Zhu et al., 2015). It had been manifested that ambient air concentrations of $PM_{2.5}$, PM_{10}, and SO_2 (p-*trend* < 0.05) were following a

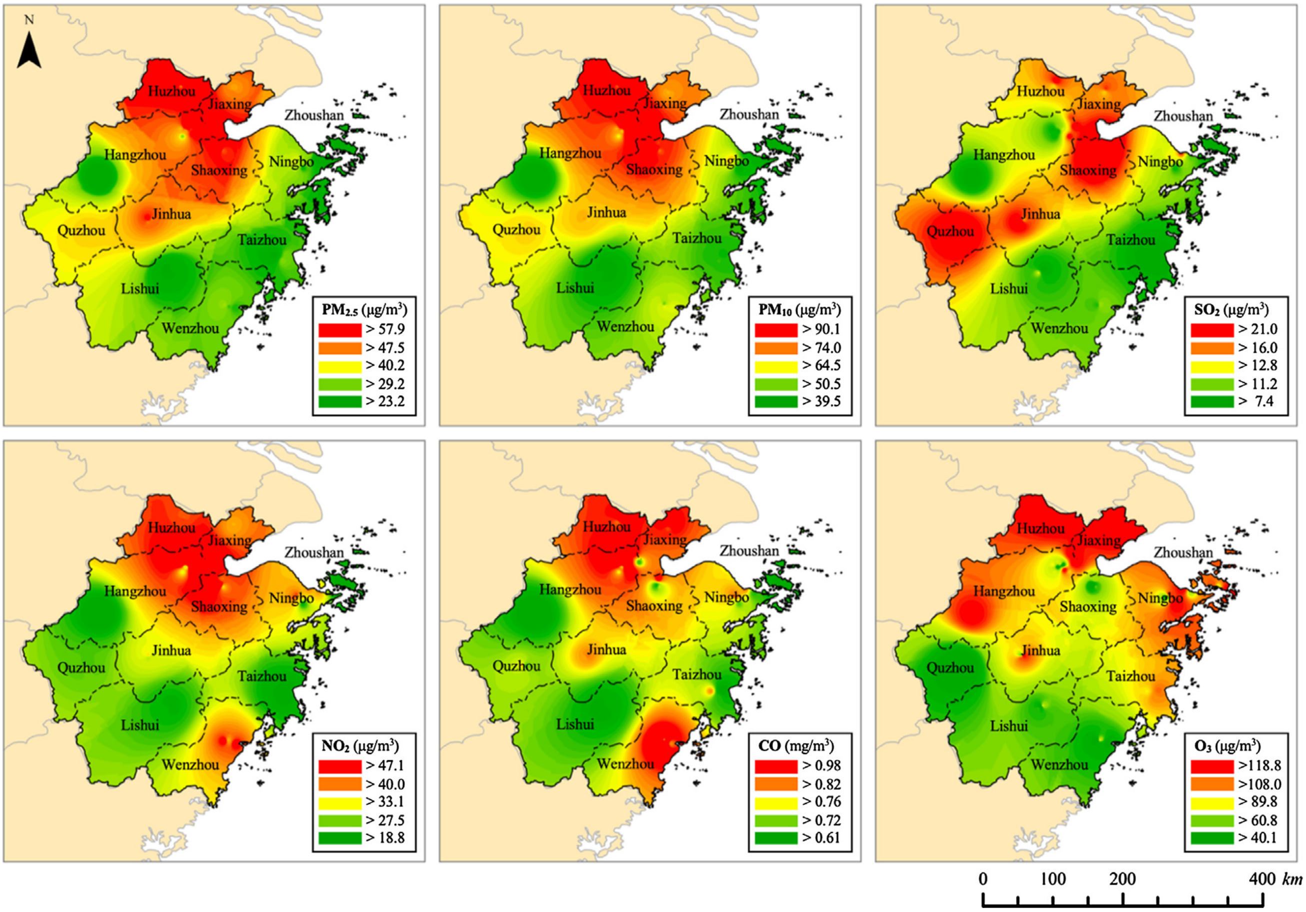

Fig. 2. Geographical distributions of concentrations for six air pollutants in Zhejiang during 2013–2017. Spatial auto-correlations of the air pollution concentrations were quantified by semivariances (Fig. A.5), and spatial interpolations were accomplished by ordinary kriging (OK) for $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO, and inversed distance weighted (IDW) estimation for O_3. The legends were stratified into five color groups by quintiles. Spatial auto-correlations were quantified by semivariograms. The pollution concentrations were firstly normalized, and then the semivariance functions were estimated by weighted least square methods, with $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO using Matérn covariate models, and O_3 using linear model. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

decreasing trend from the year 2013–2017, indicating commendable achievements of emission restriction and environmental management towards the G20 Summit held in Hangzhou in 2016. No significant variations were observed for NO_2 and CO ($p = 0.27$), however the O_3 concentrations were significantly climbing ($p = 0.02$) instead. It suggested that ambient air O_3 pollution has been turning more and more severe recently in Zhejiang Province, which should be laid more emphasis (Chen et al., 2017).

To illustrate the spatial distributions of the air pollution, the concentrations of the six ambient air pollutants were geographically mapped in Fig. 2 employing interpolation processes based on the data from the 47 monitoring stations. Obviously, large spatial variations were found for all the six pollutants, as Huzhou, Jiaxing, Shaoxing, and Hangzhou were of higher concentrations of PMs, $NO_{2,}$ and CO, while relatively low concentrations of PMs and SO_2 were observed in the cities located on the east coastline such as Ningbo, Taizhou, and Wenzhou, and NO_2 and CO aggregated in Lishui as well as the west district of Hangzhou. For SO_2, only Shaoxing and Quzhou were of higher concentrations, while for O_3, only Huzhou and Jiaxing were profoundly affected with all the other regions exposed in low concentrations. Conclusively, six air pollutants except for O_3 were apparently spatially auto-correlated by a general pattern of northern Zhejiang being of higher pollution concentrations while the south-eastern coastline districts being of better air quality, which should mainly be attributed to the uneven geographical distribution of population and industrial activities.

The personal exposure levels for the whole duration of pregnancy varied among the participants, as average maternal exposures to $PM_{2.5}$, PM_{10} and O_3 were approximately subject to normal distributions, while SO_2 and CO right-skewed, and NO_2 left-skewed, as presented in Fig. A.4 and summarized in Table A.4. In the comparisons between preterm and full-term births, maternal exposures to all six air pollutants of the pregnant mothers who finished premature deliveries were significantly higher than those who gave full-term births ($p = 0.04$).

3.3. *Preterm birth risks*

BMI, gravidity times, and gestational hypertension were strongly associated with PTB, together with all six studied air pollutants, as summarised in Table 1. Averagely by each incremental BMI value, the risks of PTB would decrease by 4.3% (OR = 0.96, $p = 0.02$, 95% CI: 0.92–0.99), so that the pregnant mothers of moderate BMI (24.6–26.8) would be of 47.6% lower PTB risks (OR = 0.52, $p < 0.001$, 95% CI: 0.39–0.68) compared to the low BMI (< 24.6) group. However, high BMI (> 26.8) pregnant mothers would be of relatively higher PTB risks than the moderate group, though still significantly lower than the low BMI group, indicating that moderately higher BMI rather than obesity could effectively be helpful in reducing the PTB risks. Every additional gravidity was related with 1.20 ($p < 0.001$, 95% CI: 1.10–1.32) relative risks of PTB. If the pregnant mothers were diagnosed with gestational hypertension, then the PTB risk would be 1.79 times higher ($p = 0.04$, 95% CI: 1.03–3.10). Other factors including age, occupation,

Table 1
Crude and adjusted odds ratios (OR) of preterm birth (PTB) with three physiological covariates and maternal average air pollutant exposures.

		Crude OR (95% CI)	*p-value*	**Adjusted*** **OR** (95% CI)	*p-value*
Covariates	**Scales**				
BMI	Low (19.1–24.6)	Ref.	Ref.	Ref.	Ref.
	Moderate (24.6–26.8)	0.52 (0.40, 0.68)	< 0.001	0.52 (0.39, 0.68)	< 0.001
	High (26.8–33.2)	0.77 (0.60, 0.98)	0.03	0.75 (0.59, 0.96)	0.02
	Per increment	0.97 (0.93, 1.00)	0.07	0.96 (0.92, 0.99)	0.02
Gravidity	Per time	1.19 (1.08, 1.30)	< 0.001	1.20 (1.10, 1.32)	< 0.001
HBP	Yes/No	1.74 (1.01, 3.00)	0.05	1.79 (1.03, 3.10)	0.04
Pollutants	**Concentration Levels**				
$PM_{2.5}$	Tertile 1 (19.1–56.3 μg/m^3)	Ref.	Ref.	Ref.	Ref.
	Tertile 2 (56.3–66.2 μg/m^3)	1.37 (1.07, 1.75)	0.01	1.30 (1.01, 1.66)	0.04
	Tertile 3 (66.2–87.6 μg/m^3)	1.79 (1.37, 2.33)	< 0.001	1.76 (1.35, 2.29)	< 0.001
	Per 10-μg/m^3 increment	1.15 (1.05, 1.27)	0.003	1.13 (1.03, 1.25)	0.007
PM_{10}	Tertile 1 (34.3–87.2 μg/m^3)	Ref.	Ref.	Ref.	Ref.
	Tertile 2 (87.2–103.0 μg/m^3)	1.35 (1.06, 1.72)	0.01	1.30 (1.02, 1.65)	0.04
	Tertile 3 (103.0–146.3 μg/m^3)	1.76 (1.22, 2.54)	0.002	1.75 (1.21, 2.52)	0.003
	Per 10-μg/m^3 increment	1.11 (1.04, 1.78)	0.001	1.17 (1.06, 1.30)	0.004
SO_2	Tertile 1 (5.9–15.2 μg/m^3)	Ref.	Ref.	Ref.	Ref.
	Tertile 2 (15.2–19.7 μg/m^3)	1.16 (0.84, 1.60)	0.36	1.20 (0.88, 1.64)	0.31
	Tertile 3 (19.7–46.4 μg/m^3)	1.84 (1.30, 2.59)	0.001	1.75 (1.12, 2.74)	0.01
	Per 10-μg/m^3 increment	1.37 (1.09, 1.70)	0.006	1.32 (1.06, 1.64)	0.001
NO_2	Tertile 1 (8.9–48.3 μg/m^3)	Ref.	Ref.	Ref.	Ref.
	Tertile 2 (48.3–55.7 μg/m^3)	1.27 (0.99, 1.62)	0.06	1.24 (1.03, 1.49)	0.03
	Tertile 3 (55.7–65.7 μg/m^3)	1.49 (1.14, 1.93)	0.003	1.48 (1.13, 1.92)	0.004
	Per 10-μg/m^3 increment	1.26 (1.12, 1.41)	< 0.001	1.19 (1.08, 1.31)	< 0.001
CO	Tertile 1 (358.7–918.0 μg/m^3)	Ref.	Ref.	Ref.	Ref.
	Tertile 2 (918.0–1039.6 μg/m^3)	1.26 (0.98, 1.63)	0.07	1.33 (0.96, 1.82)	0.08
	Tertile 3 (1039.6–3006.6 μg/m^3)	1.30 (1.01, 1.68)	0.04	1.50 (1.10, 2.05)	0.01
	Per 0.1-mg/m^3 increment	1.03 (0.98, 1.08)	0.30	1.03 (1.01, 1.05)	0.01
O_3	Tertile 1 (34.1–88.6 μg/m^3)	Ref.	Ref.	Ref.	Ref.
	Tertile 2 (88.6–99.7 μg/m^3)	1.33 (0.96, 1.84)	0.09	1.40 (1.08, 1.81)	0.01
	Tertile 3 (99.7–177.0 μg/m^3)	1.45 (1.08, 2.03)	0.02	1.49 (1.16, 1.91)	0.003
	Per 10-μg/m^3 increment	1.07 (0.99, 1.16)	0.07	1.12 (1.05, 1.19)	0.001

OR, relative risk, depicted in odds ratio; CI, confidence interval; Ref., reference group in regression models; BMI, body mass index; and HBP, high blood pressure during pregnancy, also known as gestational hypertension.

Throughout the study, the exposure concentrations were treated as both continuous variables, scaled to 0.1-mg/m^3 increment for CO while 10-μg/m^3 for the other five air pollutants, and as a categorical variable by classifying the concentration level into three tertiles.

* Regression models adjusted for BMI, gravidity time, parity time, the occurrence of gestational hypertension, maternal age, occupation, and gender of the neonate.

parity times and sex of neonates, did not significantly contribute to the PTB risks according to our study.

When the exposure concentrations were classified into three subgroups as low, moderate, and high exposure by tertiles, significantly higher risks of developing PTB were firmly observed comparing high to low exposures, with high $PM_{2.5}$ exposures being of the highest risk (OR = 1.76, $p < 0.001$, 95% CI: 1.35–2.29). Maternal exposure to PM_{10} was strongly associated with PTB (OR = 1.17, $p = 0.004$, 95% CI: 1.06–1.30) when participants were suffering from every 10-μg/m^3 higher exposure concentrations, compared to which $PM_{2.5}$ was of slightly higher risks (OR = 1.13, $p = 0.007$, 95% CI: 1.03–1.25). When average SO_2 exposure concentrations during pregnancy increased by 10-μg/m^3 while other risk factors were kept constant, the risk of PTB would be 1.32 times higher ($p = 0.001$, 95% CI: 1.06–1.64). Similarly, the odds ratio of PTB was 1.19 ($p < 0.001$, 95% CI: 1.08–1.31) for every 10-μg/m^3 increment of average NO_2 exposure, 1.03 ($p = 0.01$, 95% CI: 1.01–1.05) for every 0.1-mg/m^3 increment of average CO exposure, and 1.12 ($p = 0.001$, 95% CI: 1.05–1.19) for every 10-μg/m^3 increment of average O_3 exposure, when controlling all the other factors. It should be pointed out that PTB risks of moderate exposure to SO_2 and CO were not significant statistically, though the average OR across all covered concentration ranges were positively significant, indicating discrepancies in risk effects when exposed to different levels of concentrations. According to our results, SO_2 and NO_2, the two pollutants of the narrowest variation ranges of exposure concentrations (SO_2: 5.9–46.4 μg/m^3, NO_2: 8.9–65.7 μg/m^3), were of the highest odds ratios by each 10-μg/m^3 additional exposure, indicating that special attention should be paid to the air pollutants that can cause adverse health effects even in low concentrations, which were often neglected.

Concluded from Fig. 1 and Fig. 2, PTB risks were following a similar geographical distribution pattern to the air pollutions, as northern were higher than southern regions, suggesting the spatial auto-correlations of the PTB risks were closely linked with the spatial dependences of air pollutions, which had also been confirmed by estimated OR of maternal air pollution exposure. Consequently, the LUR residuals were of rather low spatial auto-correlations as had been manifested intuitively in mapping, assisted with the significant decreasing in semivariances (Fig. A.6) from the raw risks to the residuals. The attenuation in spatial auto-correlation had also sufficiently justified the associations between risks and pollution exposures from an original geo-epidemiology perspective.

3.4. *Relative contributions*

As shown above, various covariates and exposures to different air pollutants could induce considerably different levels of the PTB risks. The relative contributions of various pollutants can better reveal the influencing weights of each pollutant individually to the PTB risks. A pragmatic approach to reasonably estimate and compare the individual risk contributions was to normalize each risk factor before performing the regressions, as summarised in Fig. 3a. We found that BMI, gravidity

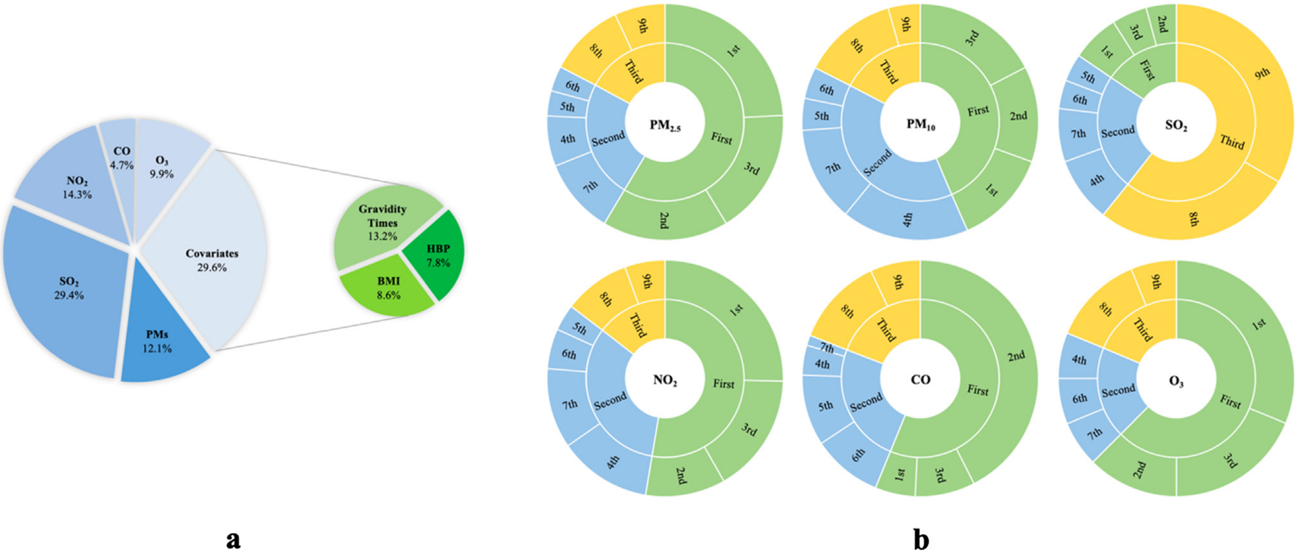

Fig. 3. Preterm birth risk contributions of ambient air pollution exposures and the covariates for the whole gestational periods (a) and each maternal trimester and month (b). The risk contributions from maternal exposures to various air pollutants (particulate matters (PMs), $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3) of each gestational month were estimated by means of normalised multiple time-to-event logistic regression model after adjusting the age, BMI, gravidity and parity times, high blood pressure, occupation, and gender of the neonates, as presented in two-level sun-burst charts. In Fig. 3a, the inner ring indicated the relative importance of each trimester, while the outer ring represented the relative contribution of each maternal month.

times, and gestational hypertension contributed a small proportion to PTB risks (29.6%). Thus, maternal air pollution exposure contributed to 70.4%. Among the contributions from pollutant exposures, SO_2 contributed the most with the proportion of 29.4%, which is more than twice of the PM exposure (12.1%), while CO exposure contributed the least by 4.7%, and the relative contributions of NO_2 and O_3 were also lower than those of SO_2, indicating that gestational SO_2 exposure should be controlled with priority since its high-risk contribution, and also its lower environmental pollution concentrations than all the other air pollutants which had resulted in the lack of population vigilance.

It has been verified that exposure to various ambient air pollutants in different gestational windows, as widely divided as the first trimester (1st to 3rd month), second trimester (4th to 7th month), and third trimester (after 8th month) of the whole gestation process, will be of different risk potentials (Ha et al., 2001, 2014; Li et al., 2017; Liu et al., 2019; Sagiv et al., 2005). For instance, some previous studies have revealed that the exposures to ambient air pollutants during the first and third trimesters are more correlated with the occurrences of PTB (Liu et al., 2019; Michelle and Beate, 2005). Hence in this study, the variations of the exposure risks by trimester (Table A.5) and by month (Table A.6) have both been estimated. For the $PM_{2.5}$, PM_{10}, NO_2, CO, and O_3, the PTB risks were significantly associated with the first trimester's exposures, with the OR of 1.008, 1.005, 1.014, and 1.005, respectively ($p < 0.05$). For SO_2, the PTB risk was statistically correlated with the exposure during the third trimester with the OR of 1.630 ($p < 0.05$). Furthermore, monthly risk relative contributions for different air pollutant exposures were calculated and perceptibly illustrated in Fig. 3b. It could be concluded that the PTB risks were mostly related to ambient air pollution exposures in the first and third gestational trimester. Maternal exposures to $PM_{2.5}$, PM_{10}, NO_2, CO, and O_3 in the first trimester occupied 43.5–62.5% of PTB risks. For the SO_2 exposure, the PTB risk was significantly related to the third-trimester exposure ($OR = 1.63$, $p = 0.002$, 95% CI: 1.14–2.33), which contributed 60.6% to PTB occurrences.

Exploring at length into monthly exposures, the risk evaluation results were mostly consistent with trimester-based estimations. The exposure of $PM_{2.5}$, PM_{10}, NO_2, and O_3 during the first and third months, as well as PM_{10} and SO_2 near the eighth pregnant month, were mostly more associated with PTB risks compared with other periods ($p < 0.05$). Though some discrepancies can be found when comparing with previous studies for the exposure windows, it could still be concluded that the exposures in the first and final gestational trimesters were the most dangerous for embryonic development, suggesting the pregnant mothers avoid high exposures to the ambient air pollution during these periods.

3.5. *Concentration-response relationships*

Establishing the concentration-response model for the associations between health outcomes and pollutant exposure is a widely recognized approach to estimate the concentration-specific relative risks (Burnett et al., 2014). Empirically, the risk associations between maternal air pollution exposures and abnormalities in delivery were not always following a linear model; instead, the increasing rate of OR would be lower among higher-level exposed population (Liu et al., 2019), based on which the concentration-response curves were accomplished in virtue of the combination of restricted cubic spline regression and curve-fitting regression models. The logistic-shaped curve model was finally selected for all air pollutants and plotted in Fig. 4, from which it could be concluded that the risks would monotonically ascend with increasing of exposure concentrations. Besides, the exposure thresholds, defined as LOAEL (lowest observed adverse effect level) in our study, of all six types of air pollutants were also derived from the curves, as 44.3, 65.1, 18.5, 27.3, 2038.8 and 108.3 $\mu g/m^3$ respectively for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3, all of which were lower than the national guideline standards for ambient air quality (MEP, 2012), indicating the pregnant be regarded as the more vulnerable population. Thus, mothers should care more about their living environments and avoid moderate to high exposures when pregnant.

3.6. *Resolving the statistical collinearity*

The maternal exposure concentrations of six studied air pollutants during pregnancy were most highly correlated with each other as stated in Table A.7, so that if all six pollutants were together added into the regression models, severe collinearity would be generated to complicate the models and thus the risk associations could be unstable and incredible more or less. Alternatively, we put forward two innovative

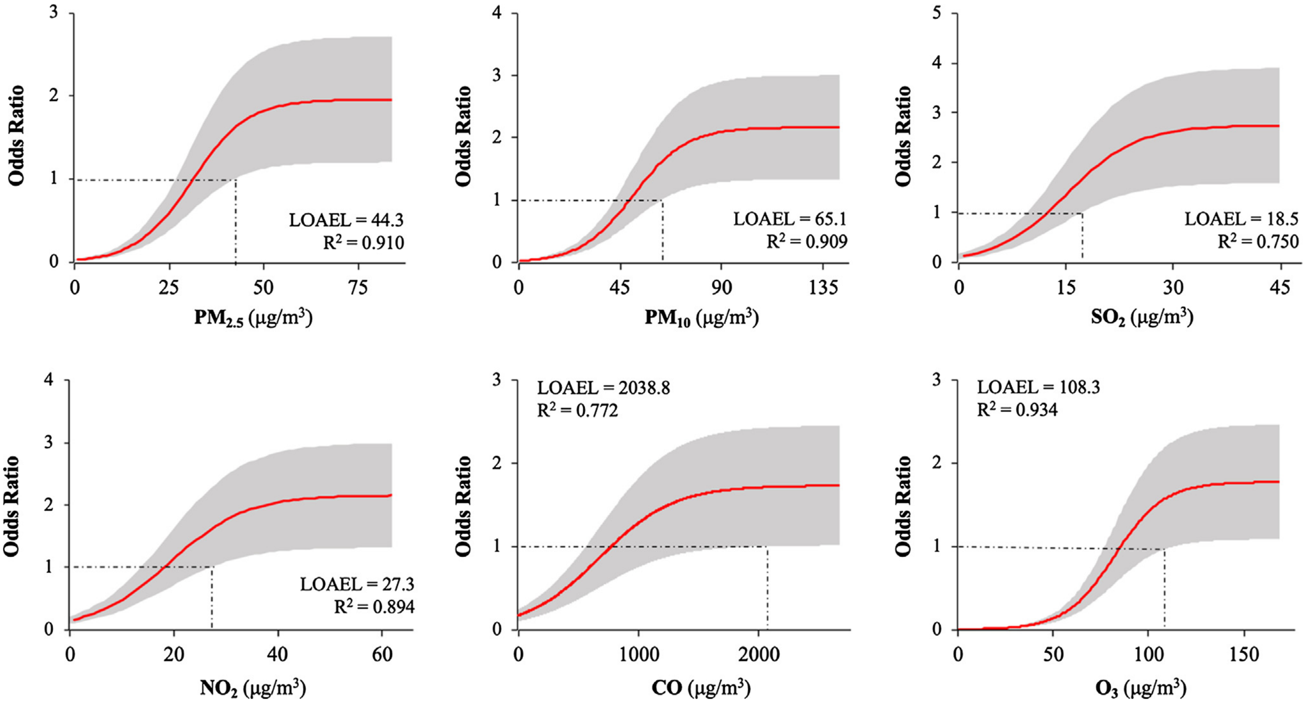

Fig. 4. Concentration-response curves for estimating preterm birth risks from ambient air pollution exposure concentrations. The curves in red were plotted using a hybrid method: restricted cubic spline regression and logistic-shaped curve-fitting regression, with 95% confidence intervals (CI) also estimated in grey shades. Fitting qualities were indicated by R^2, together with the threshold exposure concentrations depicted in LOAEL (lowest observed adverse effect level) indicated by the odds ratio (OR) started to be significantly higher than 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

feasible approaches to handle the issue.

(i) **Quasi-AQI Model.** For the more sensitive population - pregnant mothers, we took advantage of the concept of air quality index (AQI) which could synthesize the multiple air pollution concentrations into an integrated index, avoiding the interference among different air pollutants' impacts on the health risk assessments. Likewise, we defined the "quasi-AQI" for exposure assessment by integrating the gestational exposure concentrations into a single value, sharing the same calculation procedures with AQI (seen in Supplementary Materials) as indicated in Table A.8, but using the average gestational "exposure" concentrations instead of "environmental" pollution concentrations. Among our studied participants, the quasi-AQI were averaged to 82.1 ± 12.7 (IQR: 72.3–91.6, Range: 43.6–115.7), and roughly subject to a normal distribution as shown in Fig. 5a. Following the classification of AQI, most (92.6%) of the participants were moderately (quasi-AQI: 50–100) exposed to air pollutions, with 7.2% exposed to a level vulnerable to the sensitive population (quasi-AQI: 100–150), and only 0.3% living in satisfactory environments (quasi-AQI $<$ 50). After adjusting the covariates, every 10-unit increment of quasi-AQI was responsible for 8.7% increasing of PTB risks (OR = 1.09, p = 0.04, 95% CI: 1.01–1.18). The LOAEL, which was observed to be 45.9 (Fig. 5b), should be considered to be used as the guideline level for the living environments of the pregnant mothers, as they were much more vulnerable to ambient air pollution exposures according to our study outcomes.

(ii) **PCA-GLM Analysis.** However, quasi-AQI could only be used in a situation where six air pollutants (or some of them) were studied while no other pollutants were included, which narrowed the application, since, for many environmental-epidemiological studies, more pollutants would often be studied. Principal component analysis (PCA) combined with generalized linear models (GLM) was suggested as original concentrations of various raw pollutants could be re-assembled into fewer integrated new variables which were no longer correlated with each other at all. After PCA-based dimensional reduction, 3 new variables were generated by maintaining 86.6% of total raw variances, and over 75% for each variable was extracted. The first variable was highly correlated with $PM_{2.5}$, PM_{10}, SO_2, and NO_2, thus we rename it as the *prime factor*; the second variable was mainly related to CO, so that was renamed as *carbon monoxide factor*; the third variable was primely correlated with O_3, so that was renamed as *ozone factor* (Fig. 5c). Using these 3 new variables as risk factors for binary logistic regression, we found that all 3 integrate factors: *prime factor* (OR = 1.15, p = 0.008, 95% CI: 1.04–1.27), *carbon monoxide factor* (OR = 1.11, p = 0.04, 95% CI: 1.01–1.23) and *ozone factor* (OR = 1.15, p = 0.04, 95% CI: 1.01–1.31) were significantly associated with PTB risks after adjusting covariates, with Hosmer-Lemeshow test indicating no evidence of lack of fitness (p = 0.17), suggesting PCA-GLM analysis a commendable approach to solve the collinearity issues when various influencing factors were involved.

In all, though we still kept the traditional multivariate time-to-event logistic regression method to make our results comparable to previously published studies, we would recommend the two new approaches which can better handle the statistical collinearity issues in future similar studies.

4. Merits and implications

There are several merits of this study. First, different from many previous relevant studies using case-control frameworks to estimate the risk associations, our research programme was a prospective study, enrolling participants as they come without any subjective selection, so that the recruited PTB cases were representative of the whole population, and thus the estimated risks can directly reflect the prevalence of PTB, which were of more realistic implications. Second, this is one of

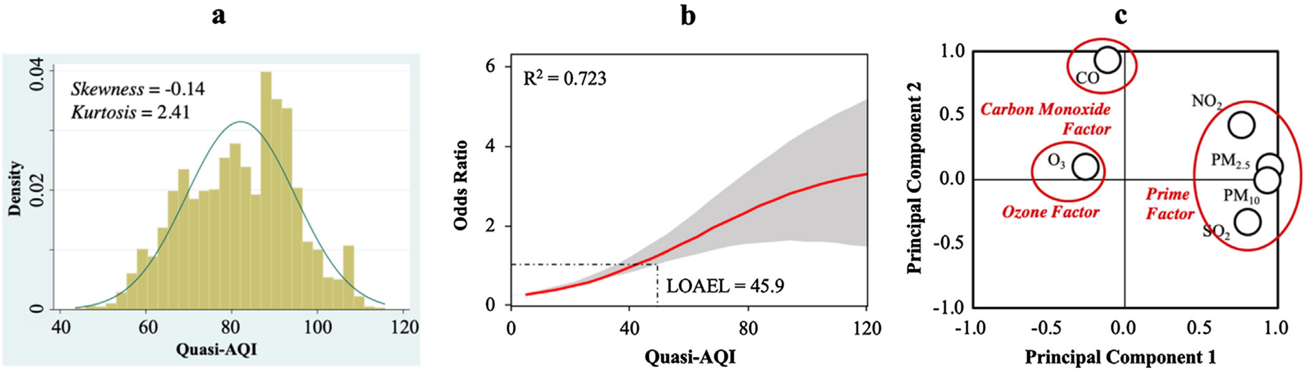

Fig. 5. Statistical distribution of population quasi-AQI (a), the exposure-response curve for preterm birth (PTB) risks based on quasi-AQI metrics (b), and component loading plot of PCA-based dimensional reduction generated new variables (c). The statistical distribution of the quasi-AQI value for the studied population was presented in the histogram and a normal distribution density curve estimated using Bayesian Gaussian model using bandwidths of 0.05 deviations, with skewness and kurtosis estimated. The exposure-response relationship was developed by a combination of restricted cubic spline regression and logistic-shaped curve-fitting model, with 95% CI indicated in grey shadows. The threshold exposure level, defined as LOAEL (lowest observed adverse effect level) in this model referring to the quasi-AQI at which the OR of PTB started to be significantly higher than 1, was 45.9. Coefficient of Kaiser-Meyer-Olkin test was 0.745, and significance of Bartlett sphericity test was < 0.05, indicating a strong correlation between air pollution concentrations and the dataset was suitable for PCA. Component loading plot was graphed in two dimensions, rotated for varimax with Kaiser normalization.

the scarce environmental-epidemiology studies taking the spatial dependences into consideration, which was more credible in checking the reasonability of the regression models. Third, our research was the first study suggesting using original statistical approaches, as quasi-AQI model, PCA-GLM method, and combination of cubic spline regression models and logistic-shaped curve-fitting regression models to establish the concentration-response relationship curves, aiming at extrapolating the uncovered exposure concentrations as well as exploring some latent environmental factors (e.g. *prime factor*, *ozone factor*, and *carbon monoxide factor*) to estimate the PTB risks, which were of both experiential and methodological significances. Last but not the least, we evaluated the relative contributions of different ambient air pollutants during different gestational windows to the PTB risks and provided better suggestions for the pregnant mothers to avoid the most dangerous exposure factors. In future similar researches, we plan to develop individual-based integrated exposure assessment instead of ground-based monitoring records as surrogates, and collect more features of the participants for risk analysis, such as smoking histories, daily activity patterns and dietary styles, only to mention a few.

This 5-year large scale study was of significant realistic implications, as the analysis results will be able to provide the pregnant mothers with pertinent suggestions for healthy deliveries. As all studied pollutants were of adverse effects on reproductive health, pregnant mothers are suggested to always check the ambient air pollution monitoring reports before going for outdoor activities, especially in the first and third trimesters. For the *prime factor* (combination of PMs, SO_2, and NO_2) exposure, the household exposures should attract more awareness since the indoor daily activities like cooking and heating activities can produce way more air pollutants, so that the pregnant should be prevented from being exposed to these common emission sources (Chen et al., 2016). Since SO_2 exposure can induce much higher PTB risk, the pregnant mother's healthy deliveries in rural areas where using coal during cooking and heating processes and northern China where has higher SO_2 concentration in ambient air are expected to be more affected.

Besides controlling the personal exposure to ambient air pollutants, there are some other actions that the pregnant can take to lower the risk of abnormal delivery. First, the awareness of using contraceptive measures and equipment scientifically should be elevated to hedge any unexpected pregnancy. Second, regularity in work and rest patterns, as well as healthy dietary patterns, are strongly recommended to reduce the possibility of developing high blood pressure or diabetes during pregnancy. Third, the pregnant should be supplied with nutrition sufficiently before and during pregnancy to increase the BMI by elevating the body weight.

5. Conclusions

The six air pollutants: $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3, in Zhejiang Province were mostly at safe levels according to the national guideline standard, and generally following a decreasing trend from 2013 to 2017 except for O_3, which was climbing instead. Relatively higher air pollutions were mainly aggregated in north regions of Zhejiang, where PTB cases were also more reported. Gestational exposure to the six air pollutants together with multiple gravidity times and gestational hypertension contributed to the occurrences of PTB, while higher BMI could compromise the PTB risks. The risks elevated with the increase of air pollution exposure levels, especially the SO_2, which contributed the largest to PTB risks. As a sensitive population, the PTB threshold gestational exposure concentrations of six studied air pollutants for the pregnant mothers were all lower than the suggested national ambient air quality, suggesting the national standard safe-line of air pollution exposure should be stricter; and the first and third trimester exposure was the most vulnerable period that the pregnant should pay special attention to. In addition to filling the literature gap of PTB risks owing to maternal air pollution exposures in developed regions of China, this study also provided innovative approaches to handle collinearities in multi-pollutant environmental-epidemiological studies, which also contributed methodologically to the literature.

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Competing interests

No competing interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105242.

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