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Identifying windows of susceptibility for maternal exposure to ambient air pollution and preterm birth

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ABSTRACT

Maternal exposure to ambient air pollution has been associated with preterm birth (PTB), however, entire pregnancy or trimester-specific associations were generally reported, which may not sufficiently identify windows of susceptibility. Using birth registry data from Guangzhou, a megacity of southern China (population ~14.5 million), including 469,975 singleton live births between January 2015 and July 2017, we assessed the association between weekly air pollution exposure and PTB in a retrospective cohort study. Daily average concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 from 11 monitoring stations were used to estimate district-specific exposures for each participant based on their district residency during pregnancy. Distributed lag models (DLMs) incorporating Cox proportional hazard models were applied to estimate the association between weekly maternal exposure to air pollutant and PTB risk (as a time-to-event outcome), after controlling for temperature, seasonality, and individual-level covariates. We also considered moderate PTB (32–36 gestational weeks) and very PTB (28–31 gestational weeks) as outcomes of interest. Hazard ratios (HRs) and 95% confidential intervals (95% CIs) were calculated for an interquartile range (IQR) increase in air pollutants during the study period. An IQR increase in $PM_{2.5}$ exposure during the 20th to 28th gestational weeks (27.0 μg/m^3) was significantly associated with PTB risk, with the strongest effect in the 25th week (HR = 1.034, 95% CI:1.010–1.059). The significant exposure windows were the 19th–28th weeks for PM_{10}, the 18th–31st weeks for NO_2, and the 23rd–31st weeks for O_3, respectively. The strongest associations were observed in the 25th week for PM_{10} (IQR = 37.0 μg/m^3; HR = 1.048, 95% CI:1.034–1.062), the 26th week for NO_2 (IQR = 29.0 μg/m^3; HR = 1.060, 95% CI:1.028–1.094), and in the 28th week for O_3 (IQR = 90.0 μg/m^3; HR = 1.063, 95% CI:1.046–1.081). Similar patterns were observed for moderate PTB (32–36 gestational weeks) and very PTB (28–31 gestational weeks) for $PM_{2.5}$, PM_{10}, NO_2 exposure, but the effects were greater for very PTB. We did not observe any association between pregnancy SO_2 exposure and the risk of PTB. Our results suggest that middle to late pregnancy is the most susceptible air pollution exposure window for air pollution and PTB among women in Guangzhou, China.

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1. Introduction

Preterm birth (PTB) is defined as births delivered < 37 completed gestational weeks. According to the World Health Organization (WHO) estimates, the incidence of PTB ranges from 5% to 18% across 184 countries (Dimes et al., 2012). PTB is a leading cause of neonatal morbidity and mortality (Liu et al., 2016), and is associated with long-term physical, cognitive, and developmental problems (Dimes et al., 2012), which collectively place a substantial burden on affected families, as well as healthcare, education, and social services (Petrou, 2003).

The mechanisms involved in PTB are complex (Goldenberg et al., 2008) and are not been fully understood. Recently, there has been a growing interest in evaluating the impacts of exposure to environmental risk factor during pregnancy on PTB. Ambient air pollution has been the focus of numerous studies because it can induce systemic inflammation, oxidative stress, and hemodynamic changes (Kannan et al., 2006; Schlesinger et al., 2006).

Previous studies have examined the association between a number of pollutants and PTB, and many of them attempted to identify windows of susceptibility during pregnancy (Jacobs et al., 2017; Li et al., 2017; Shah et al., 2011; Stieb et al., 2012). Identifying susceptible windows can assist in defining the underlying mechanisms and guiding prenatal care (e.g., behavioral strategies to avoid air pollution) (Ritz and Wilhelm, 2008; Woodruff et al., 2009). Among previous studies, trimester, entire pregnancy, or specific months were the most common time period of interest, however, the findings are inconsistent. For example, $PM_{2.5}$ exposure during the first trimester (Pereira et al., 2014; Ritz et al., 2007), or the third trimester (DeFranco et al., 2016; Hannam et al., 2014) was shown to be associated with PTB. Some studies observed PM_{10} during the second trimester (Hannam et al., 2014), NO_2 during the first trimester (Ritz et al., 2007), SO_2 during the last month (Le et al., 2012; Liu et al., 2003), or O_3 exposure during the first (Ha et al., 2014; Lee et al., 2013), second and entire pregnancy (Ha et al., 2014) increased the risk of PTB. One study reported significant associations between $PM_{2.5}$, NO_2, and O_3 exposure during any trimester and PTB (Lavigne et al., 2016). Other studies did not observe such significant associations between air pollution and PTB (Brauer et al., 2008; Chang et al., 2011; Hyder et al., 2014). The trimester-specific association may be insufficient to identify susceptible window because the biological response to air pollution exposure may not align with trimesters exactly. A recent study estimated critical windows for maternal air pollution in children's health and found that in the case of potential windows of susceptibility spanning multiple trimesters, the trimester-specific association may be biased and lead to incorrect window identification (Wilson et al., 2017). The authors proposed that estimating weekly-specific associations using a distributed lag model (DLM) could help to obtain less biased estimates.

Given air pollution exposure is time-varying and may result in time-varying, cumulative as well as delayed effects on reproductive health (Ritz and Wilhelm, 2008; Woodruff et al., 2009), DLMs, a data-driven method allowing for modeling risk that depends on both the intensity and timing of past exposures, are applicable for identifying windows (Chang et al., 2015; Gasparrini, 2014). In addition, DLMs allow for incorporating regression models, such as generalized linear models (GLMs), Cox proportional hazard models, and generalized additive models (GAMs) to estimate the associated parameters (Gasparrini, 2014; Gasparrini et al., 2010), which adds flexibility to identify windows. Few studies have applied this strategy to assess the susceptible windows for PTB (Chang et al., 2015; Warren et al., 2012). The authors further extended their data approach by treating gestational age as time-to-event data, which can accommodate the differences in exposure length among pregnancies of different gestational ages. However, such studies were conducted in areas with relatively low air pollution concentrations. It is unclear to what extent they are relevant to areas with higher pollutant concentrations, such as China. To our knowledge, no published studies have used this data approach to identify the windows of susceptibility for maternal exposure to ambient air pollution and preterm birth in China.

Moreover, according to the WHO recommendations, PTB is further categorized into moderate PTB (32 to 36 completed weeks of gestation), very PTB (28 to 31 completed weeks), and extremely PTB (< 28 completed weeks) (WHO, 2012). This classification is important for neonatal prognoses, and different risk factors have been associated with different subtypes of PTB (Moutquin, 2003), including air pollution exposure (Ha et al., 2014; Symanski et al., 2016; Wang et al., 2018b; Wu et al., 2009; Zhao et al., 2015). However, the role of susceptible windows on different PTB subtypes is unclear.

In this study, we treated gestational age as a time-to-event outcome and applied DLMs incorporating Cox proportional hazard models to investigate the association between weekly air pollution exposure and PTB in China, with an exploration of the susceptible exposure windows, including for different PTB subtypes.

2. Methods

2.1. Population

The study population for this retrospective cohort study was identified from the Birth Registry System in Guangdong province, China, which commenced and then was refined in 2014. The present study included mothers and their singleton live births in the capital city Guangzhou (population ~14.5 million) from January 1, 2015 to July 31, 2017 (N = 506,280), covering all newborns delivered in hospitals (98.87%), maternity and child care institutions (1.05%), and at homes or other non-medical facilities (0.08%). Collected variables included the pregnant women's home address during pregnancy, maternal age, paternal age, parity, medical conditions during pregnancy (including placenta abruption, placenta previa, placental accreta, pregnancy-induced hypertension, preeclampsia, eclampsia, oligohydramnios, uterine rupture, and gestational diabetes), delivery mode, gestational age at birth, date of birth, birth weight, and infant sex. There was no data on smoking but prevalence in pregnant Chinese women is very low (3.8%) (Xu et al., 2017).

For a retrospective cohort study with a fixed start and end date, there is a potential for “fixed cohort bias” (Strand et al., 2011b), which occurs by including only the longer pregnancies at the start of the study and only the shorter pregnancies at the end of the study. In order to limit the potential for this bias, we included the women whose conception dates were between 28 weeks before the cohort started (January 1, 2015), and 44 weeks before the cohort ended (July 31, 2017) (N = 470,192 mother-infant pairs). According to the average age at menarche (12.8 years) (Song et al., 2011) and natural menopausal age (50.8 years) (Shao et al., 2014) in the Chinese population, we excluded 39 pairs with an outlier maternal age (< 13 or > 50 years).

2.2. Preterm birth outcomes

The gestational age (week) was determined by combining mother-reported last menstrual period and ultrasound examination to represent the best available clinical estimate for each woman. When available, ultrasound estimates were used; otherwise, the date of the last menstrual period was used. PTB was defined as delivery prior to 37 completed weeks of gestation (Beck et al., 2010). According to WHO recommendations (WHO, 2012), we further classified PTB into moderate PTB (32 to 36 completed weeks of gestation) and very PTB (28 to 31 completed weeks). There was a very small number of extremely PTB (< 28 completed weeks, n = 178) in our population. Because of this small number, we did not include these births, and the final sample size for the analysis was 469,975.

This study was approved by the medical ethics committee of the School of Public Health, Sun Yat-sen University. Data used in the study

were anonymous and there was no individually identifiable information.

2.3. Exposure assessment

There are 11 geographic districts in Guangzhou (Fig. S1), the size of the districts ranges from 39 km^2 to 1975 km^2, with a mean of 676 km^2 (http://www.gzstats.gov.cn). The available maternal residential address during pregnancy was at the district level in the registry. There are 11 Air Quality Monitoring Stations operated by the State Environmental Protection Administration of China in Guangzhou (Fig. S1). Except for Nansha, Zengcheng, Haizhu, and Huangpu district, one station in each district measured daily ambient air pollutant concentrations (in $\mu g/m^3$) for the entire study period, including particulate matter with an aerodynamic diameter ≤ 10 μm or 2.5 μm (PM_{10} and $PM_{2.5}$, respectively), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3). Two monitoring stations are located in each of Haizhu and Huangpu districts; we averaged air pollutant concentrations of the two stations for these two districts. Nansha and Zengcheng districts do not have monitoring stations, so we used the data from the nearest station in Panyu and Huangpu district to estimate levels in Nansha and Zengcheng districts, respectively. The distance from the middle of Nansha and Zengcheng districts to the nearest station is 24.7 km and 20.8 km, respectively.

The measurement of all air pollutants strictly followed Standard on Ambient Air Quality (GB 3095-2012) (http://english.sepa.gov.cn/) established by Environmental Protection Department of the People's Republic of China (renamed as “Ministry of Ecology and Environment of the People's Republic of China” since 2018) in 2012. $PM_{2.5}$ and PM_{10} were measured by the beta attenuation method; SO_2, NO_2, and O_3 were measured using fluorescence, chemiluminescence, and ultraviolet photometry, respectively.

Between 2014 and 2017, 0.76%–1.98% of daily air pollutant values were missing among 10 stations. The 11th station began monitoring air pollution from June 2015, for which, 0.51% of days have missing values through to 2017. If a daily value from a monitoring station was missing, the mean of the two closest values within 7 days before and after the missing data were used to impute the missing value.

We assigned daily air pollution exposure for each subject using district-specific daily $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 according to residential address during pregnancy. We then derived weekly air pollution by averaging the daily mean concentration on the first day of the corresponding gestational week and the following 6 days (Wang et al., 2018a). Gestational age was treated as a time-to-event outcome, and term births were censored at week 37. For each pregnancy, the weekly exposure from the week at delivery (for PTBs) or from the 37th week (for term births) backward to the week of conception was calculated.

Daily mean temperature (°C) was collected from the China Meteorological Data Service Center (http://data.cma.cn/). We used the same approach to assign ambient temperature exposure for each pregnancy as we did for air pollutants.

2.4. Statistical analyses

Pearson's correlation was used to examine the correlation among $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 in 11 districts from 2014 to 2017.

We applied distributed lag models (DLMs) incorporating with Cox proportional hazard models to estimate the exposure-lag-response association between weekly-specific maternal air pollution exposure and PTB by accounting for all the past (lagged) exposures (Gasparrini, 2014; Wu et al., 2018). This class of models can describe complex exposure-lag-association by creating a flexible “cross-basis” function, which simultaneously defines the conventional exposure-response association and the additional lag-response association (Gasparrini, 2014).

In this study, we used a linear function to model the exposure-response relationship of air pollutant exposure with PTB. Cox proportional hazard models were applied to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for per interquartile range (IQR) increase in concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 during the period (2014–2017), respectively (Wu et al., 2018).

For the lag-response relationship, we assumed that the association between exposure and outcome varies smoothly across weeks (Wilson et al., 2017; Wu et al., 2018). Natural cubic splines were applied for each pollutant by varying degrees of freedom (dfs) from 3 to 10. Since several studies have highlighted the existence of short-term effects of air pollution exposure on PTB (Jiang et al., 2007; Schifano et al., 2013), we set knots at equally space of the lag range on a log scale to capture more precisely such variability in the last weeks of gestation. The optimal df was selected based on minimum Akaike Information Criterion (AIC) (Gasparrini, 2014). Finally, dfs selected for lag distribution were 7 for $PM_{2.5}$, 7 for PM_{10}, 6 for NO_2, 3 for SO_2, and 5 for O_3.

All the models were adjusted for the covariates, including maternal age, parity, season of conception (spring: March–May; summer: June–August; fall: September–November; winter: December–February), medical conditions during pregnancy (yes if having any of the following conditions: placenta abruption, placenta previa, placental accreta, pregnancy-induced hypertension, preeclampsia, eclampsia, oligohydramnios, uterine rupture, and gestational diabetes), delivery mode, and infant sex. Both high and low temperature during pregnancy might be associated with adverse birth outcomes (Strand et al., 2011a). Mean ambient temperature during the entire pregnancy were included with natural cubic splines of 3 dfs (Chen et al., 2018). Also, districts were fitted as a random effect in the models to account for potential clustering and spatial patterns.

Weekly-specific association between air pollution and moderate PTB, very PTB was assessed as we did for overall PTB, except that exposure period was confined to gestational weeks 1 to 32 for very PTB.

We estimated cumulative effects for three trimesters (weeks 1–12; weeks 13–27; weeks 28-birth (for PTBs) or weeks 28–37 (for term births)) and the entire pregnancy as most previous studies did. HRs and 95% CIs were calculated for per IQR (during the study period 2014–2017) increase in each pollutant, with adjustment for previous exposure, and the aforementioned covariates.

2.5. Sensitivity analyses

Sensitivity analyses were performed to examine the robustness of the results. We included two pollutants in the model one by one as well as added multi-pollutants simultaneously to evaluate the effects of air pollution on PTB. $PM_{2.5}$ and PM_{10} were not concurrently included in one model because of their high correlation. We also added back the births between 20 and 28 weeks (extremely preterm births) into overall PTB to evaluate their association with air pollution. In order to evaluate the influence of variation of air pollution cross districts on effect estimation, we repeated our analyses by excluding the births from the smallest and largest districts. Due to the lack of information to distinct spontaneous and medically indicated PTB, we performed sensitivity analyses by restricting to vaginal births and the births without medical conditions during pregnancy, respectively. We also added analyses by setting knots at equal space of the original lag range, not on a log scale.

All analyses were performed with SAS 9.4 (SAS Institute, Inc., Cary, NC) and R 3.4.4 (R Development Core Team 2018), and packages “dlnm”, “splines”, and “survival” in R software were used (Gasparrini, 2014).

3. Results

Of the 469,975 singleton live births in the study, 25,879 (5.51%) were overall PTBs. Among all PTB, moderate and very PTB account for 23,895 (92.2%) and 1984 (7.7%) of the study population, respectively.

Table 1 shows the distribution of selected characteristics among our study population. Older parents were more likely to have PTBs.

Table 1
Summary characteristics of participants.

Characteristics	Preterm birth (< 37 weeks) n = 25,879	Term birth (≥ 37 weeks) n = 444,096	Total births n = 469,975
Gestational age (weeks, mean (SD))	34.7 (1.8)	38.9 (1.1)	38.7 (1.5)
Maternal age (years, mean (SD))	29.5 (5.5)	28.8 (5.0)	28.8 (5.0)
Paternal age (years, mean (SD))	31.9 (6.1)	31.1 (5.7)	31.2 (5.7)
Districts, n (%)			
1	2110 (8.2)	23,074 (5.2)	25,184 (5.4)
2	1884 (7.3)	35,094 (7.9)	36,978 (7.9)
3	1449 (5.6)	29,568 (6.7)	31,017 (6.6)
4	4388 (17.0)	73,918 (16.6)	78,306 (16.7)
5	431 (1.6)	12,135 (2.8)	12,566 (2.6)
6	2677 (10.3)	45,659 (10.3)	48,336 (10.3)
7	4397 (17.0)	63,073 (14.2)	67,470 (14.4)
8	2098 (8.1)	39,045 (8.8)	41,143 (8.8)
9	3008 (11.6)	62,324 (14.0)	65,332 (13.9)
10	1061 (4.1)	18,394 (4.1)	19,455 (4.1)
11	2376 (9.2)	41,812 (9.4)	44,188 (9.4)
Year of birth, n (%)			
2015	7510 (29.0)	126,827 (28.6)	134,337 (28.6)
2016	12,769 (49.3)	203,600 (45.9)	216,369 (46.0)
2017 (01 Jan–31 Jul)	5600 (21.6)	113,669 (25.6)	119,269 (25.4)
Season of conception, n (%)			
Spring	5425 (21.0)	92,078 (20.7)	97,503 (20.8)
Summer	7694 (29.7)	136,847 (30.8)	144,541 (30.8)
Fall	6558 (25.3)	115,016 (25.9)	121,574 (25.9)
Winter	6202 (24.0)	100,155 (22.6)	106,357 (22.6)
Parity, n (%)			
Primiparous	9840 (38.1)	169,745 (38.2)	179,585 (38.2)
Multiparous	12,147 (46.9)	208,825 (47.0)	220,972 (47.0)
Missing	3892 (15.0)	65,526 (14.8)	69,418 (14.8)
Medical conditions during pregnancy, n (%)			
No	5534 (21.4)	217,453 (49.0)	222,987 (47.5)
Yes	16,442 (63.5)	160,267 (36.1)	176,709 (37.6)
Missing	3903 (15.1)	66,376 (15.0)	70,279 (15.0)
Delivery mode, n (%)			
Vaginal	12,028 (46.5)	251,720 (56.7)	263,748 (56.1)
Cesarean	9960 (38.5)	126,867 (28.6)	136,827 (29.1)
Missing	3891 (15.0)	65,509 (14.8)	69,400 (14.8)
Infant sex, n (%)			
Male	15,266 (59.0)	236,636 (53.3)	251,902 (53.6)
Female	10,611 (41.0)	207,451 (46.7)	218,062 (46.4)
Missing	2 (0)	9 (0)	11 (0)

Compared to term births, PTBs were observed more frequently among mothers who conceived in spring or winter, and who had medical conditions during pregnancy. In addition, there were higher proportions of male babies and cesarean delivery among PTBs.

Between 2014 and 2017 in Guangzhou, the mean concentrations of $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 were 39.1 μg/m^3, 60.2 μg/m^3, 46.1 μg/m^3, 13.2 μg/m^3, and 112.6 μg/m^3, respectively (Table 2). $PM_{2.5}$ and PM_{10} were highly correlated with each other (Pearson's correlation coefficient: r = 0.92). Both pollutants were positively and moderately correlated with NO_2 and SO_2 (r ranged from 0.50 to 0.67) and weakly correlated with O_3 (r = 0.19 and 0.23 respectively). Correlations among NO_2, SO_2, and O_3 was low (r ranged from 0.04 to 0.35). The mean ambient temperature during the study time period was 22.1 °C and was negatively and weakly correlated with air pollutants except for O_3 (r = 0.37).

As shown in Fig.1, the risk of overall PTB was associated with $PM_{2.5}$ or PM_{10} exposure during the 20th to 28th gestational weeks, and the strongest association was observed for the 25th gestational week ($PM_{2.5}$: IQR = 27.0 μg/m^3; HR = 1.034, 95% CI:1.010–1.059 (Table S1); PM_{10}: IQR = 37.0 μg/m^3; HR = 1.048, 95% CI:1.034–1.062 (Table S2)). NO_2 exposure during the 18th to 29th gestational weeks was associated with increased PTB risk, with the corresponding peak association in the 26th week (IQR = 29.0 μg/m^3; HR = 1.060, 95%CI:1.028–1.094 (Table S3)). For O_3, there were two significant exposure windows: the 1st-5th and the 23rd-31st gestational weeks, and corresponding peak associations were observed in the 1st (IQR = 90.0 μg/m^3; HR = 1.047, 95%CI:1.026–1.070) and the 28th week (HR = 1.063, 95%CI:1.046–1.081), respectively (Table S4). A small inverse association was also observed for PM_{10}, NO_2 and O_3 exposure during early pregnancy (Tables S2–S4), respectively. We did not observe any association between SO_2 exposure and PTB.

Identified exposure windows and magnitudes of association between each air pollutant and moderate PTB were similar to those for overall PTB (Fig. 1 and Tables S1–S4).

For very PTB, the range of identified exposure windows associated with $PM_{2.5}$ and PM_{10} were narrower (the 23rd–28th gestational weeks) than overall and moderate PTB, but the association was stronger. Corresponding peak associations were observed in the 26th gestation week, with HRs (95%CIs) were 1.127 (1.060–1.198) (Table S1) and 1.104 (1.050–1.161) (Table S2), respectively. The exposure window for NO_2 and very PTB was similar as for overall and moderate PTB, and the association was also stronger (HR = 1.135, 95%CI: 1.062–1.213) (Table S3). For O_3, the exposure window was highly variable; as we only observed a weakly positive association of very PTB with exposure during the 26th–27th weeks. However, an inverse association of exposure during the 7th–18th weeks was observed (Table S4).

After adjusting for other pollutants (Figs. S2–S6), similar effects with the single-pollutant model were observed for SO_2 and O_3, while the effects of both $PM_{2.5}$ and PM_{10} exposure were attenuated when adjusted for NO_2, and the effects of NO_2 were attenuated when adjusted for $PM_{2.5}$. By adding the births between 20 and 28 weeks (extremely preterm births) back, the identified exposure windows and magnitudes of association between each air pollutant and overall PTB did not change (Fig. S7). Similar exposure-lag-response association between each air pollutant and PTB, as well as moderate PTB and very PTB, were observed after excluding the births from the smallest and largest districts (Fig. S8). By restricting to vaginal births, the main identified susceptible windows for each air pollutant remained (Fig. S9). The small inverse effects of PM_{10}, NO_2, and O_3 exposure during early pregnancy observed among all the singleton live births were attenuated. Meanwhile, positive associations occurred between $PM_{2.5}$, PM_{10}, and NO_2 exposure during early pregnancy and very PTB. Analyses by excluding the births with medical conditions during pregnancy yielded similar results as that restricted to only vaginal births,

Table 2
Summary statistics of air pollutant concentration and temperature in Guangzhou from 2014 to 2017.

Pollutants	Mean	SD	Max	75th	50th	25th	Min	IQR	$PM_{2.5}$	PM_{10}	NO_2	SO_2	O_3	Temperature
$PM_{2.5}$	39.1	22.7	214.0	50.0	34.0	23.0	1.0	27.0	1.00	0.92	0.62	0.50	0.19	−0.27
PM_{10}	60.2	31.4	295.0	75.0	53.0	38.0	2.0	37.0		1.00	0.67	0.52	0.23	−0.20
NO_2	46.1	24.2	217.0	58.0	42.0	29.0	1.0	29.0			1.00	0.35	0.04	−0.21
SO_2	13.2	8.0	171.0	16.0	11.0	8.0	1.0	8.0				1.00	0.19	−0.03
O_3	112.6	67.7	628.0	152.0	104.0	62.0	1.0	90.0					1.00	0.37
Temperature	22.1	6.2	31.1	27.4	23.7	17.4	3.4	10.0						1.00

Units are μg/m^3 for $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3; °C for ambient temperature.

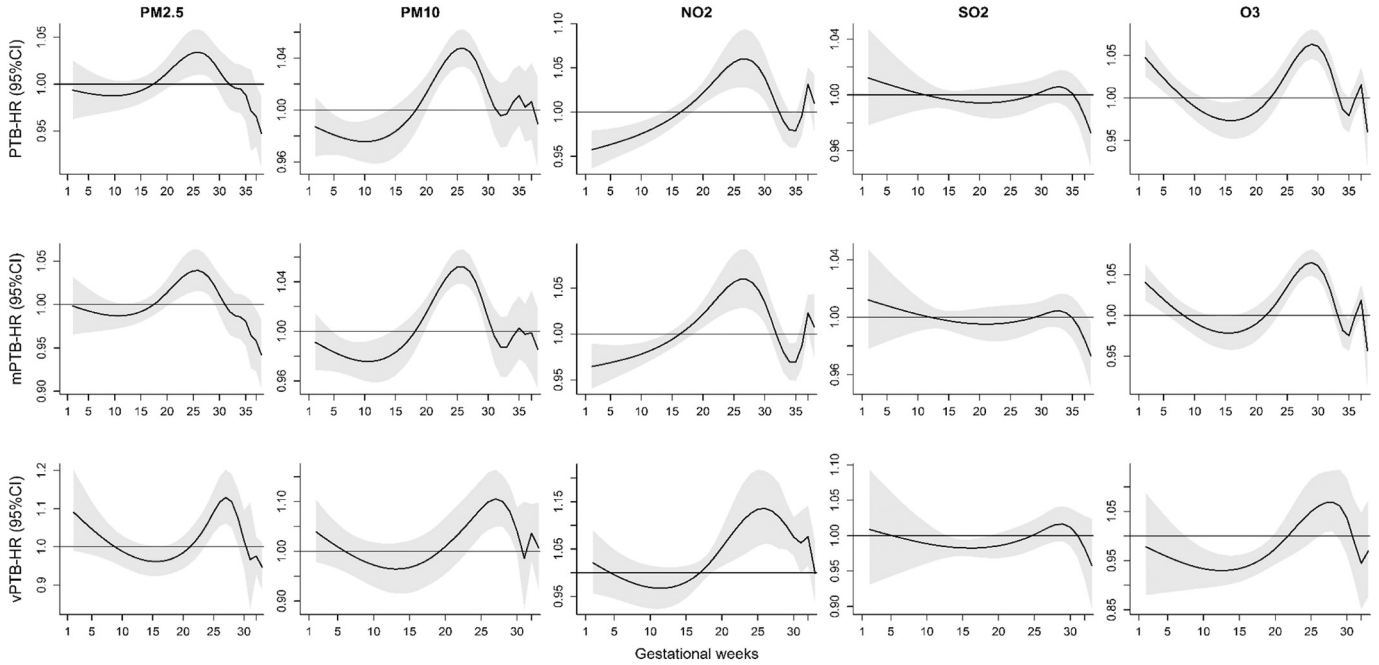

Fig. 1. Hazard ratios (HRs) of PTB, moderate (mPTB), and very preterm birth (vPTB) associated with weekly-specific air pollution exposure.
Distributed lag models (DLMs) incorporating with Cox proportional hazard models were used to calculate HRs (95%CIs) for per IQR increment (27 μg/m^3 for $PM_{2.5}$; 37 μg/m^3 for PM_{10}, 29 μg/m^3 for NO_2, 8 μg/m^3 for SO_2, and 90 μg/m^3 for O_3) during the study period (2014–2017); lag distribution was modelled as natural cubic splines with dfs of 7 for $PM_{2.5}$, 7 for PM_{10}, 6 for NO_2, 3 for SO_2, and 5 for O_3.All models adjusted for maternal age, parity, year of birth, season of conception (spring: March–May; summer: June–August; fall: September–November; winter: December–February), medical conditions during pregnancy, infant gender, and delivery method; Mean ambient temperature during the entire pregnancy was included with natural cubic splines of 3 dfs; districts were fitted as a random effects.

except for NO_2 and O_3 (Fig. S10). The effects of NO_2 and O_3 were generally attenuated and the small inverse association between O_3 exposure during early pregnancy and PTB, as well as moderate and very PTB were observed. By using equally spaced knots at the original lag range, although the shape of the association curve slightly changed (Fig. S11), we observed similar exposure windows for each pollutant: weeks 20–29 for $PM_{2.5}$, 19–29 for PM_{10}, 18–29 for NO_2, and 22–32 for O_3, respectively (Tables S5–S8). We also observed similar exposure windows for moderate and very PTB as well as the similar inverse association between exposure to PM_{10}, NO_2, and O_3 during early pregnancy and PTB.

Cumulative effects are shown in Table 3. For per IQR increase, $PM_{2.5}$ exposure during the second trimester was associated with the risk of moderate PTB (IQR = 27 μg/m^3; HR = 1.292, 95% CI: 1.017–1.641). PM_{10} and NO_2 exposure during the second trimester increased the risk of both PTB and moderate PTB, while their exposure during the first trimester decreased the risk. In addition, NO_2 exposure during the second, the third trimester, and the entire pregnancy were associated with very PTB.

4. Discussion

This large population-based retrospective cohort study in Guangzhou, a megacity of southern China found that maternal exposure to ambient $PM_{2.5}$, PM_{10}, NO_2, and O_3 during the middle to late pregnancy (from the 18th to 31st gestational weeks) was associated with the increased risk of PTB.

The prevalence of PTB in this study was 5.5%, which is lower than that reported (8.0%) by a nationwide study in China (Wang et al., 2018b). However, it is very similar to those of previous reports in Guangzhou city (5.6% for vaginal delivery, 5.2% for Cesarean delivery from 2001 to 2011 (He et al., 2016) and 5.1% to ~6.4% from 2002 to 2012 (Fu and Yu, 2011; Guo et al., 2014)). The lower rate of PTB in Guangzhou may be partially explained by the implementation of several public health programs that promoted maternal and children's health and improved access to antenatal care service (He et al., 2016). While gestational age uncertainty could also be a possible explanation if mother-reported last menstrual period was applied to determine the gestational age, it seemed unlikely in this study because the majority of the births in the study (98.87%) were delivered in hospitals where all births received antenatal care service and gestational age was further determined by ultrasound examination.

Numerous studies have examined the association between PTB and maternal air pollution exposure by trimesters (Gehring et al., 2011; Hannam et al., 2014; Hyder et al., 2014; Lavigne et al., 2016; Pereira et al., 2013; Pereira et al., 2014; Qian et al., 2016; Wang et al., 2018b; Wu et al., 2009), months (Le et al., 2012; Liu et al., 2003), or specific gestational weeks (Jiang et al., 2007; Schifano et al., 2016). Most of these studies obtained inconsistent findings in terms of susceptible exposure window, even for the same air pollutant. For example, identified exposure window for $PM_{2.5}$ and PTB were reported as the first month (Huynh et al., 2006), the first trimester (Pereira et al., 2014; Ritz et al., 2007), the third trimester (DeFranco et al., 2016; Hannam et al., 2014), as well as any trimester (Ha et al., 2014; Lavigne et al., 2016). Such inconsistency may be explained by several factors, including differences in study designs, air pollution concentration and chemical composition, demographic characteristics of the study population. These mixed approaches and findings make it difficult to conclude the potential susceptible windows of exposure.

Wilson et al. (Wilson et al., 2017) compared three strategies for estimating critical windows for maternal air pollution exposure and children's health, and suggested when the critical windows of air pollution exposure did not align with clinically defined trimesters, results based on trimester-specific association were biased and identified windows were incorrect. By applying DLMs, we observed that middle to late pregnancy is a consistent window of susceptibility across different air pollutants ($PM_{2.5}$: the 20th–28th weeks; PM_{10}: the 19th–28th weeks; NO_2: the 18th–31st weeks; O_3: the 23rd–31st weeks), with peak association observed in the 25th, 25th, 26th, and 28th week, respectively. This window spanned a large part of the second trimester and a small

Table 3
Hazard ratios (HRs) of PTB, moderate (mPTB), and very preterm birth (vPTB) associated with cumulative air pollution exposure during trimesters and the entire pregnancy.

Air pollutants	Exposure period	PTB		mPTB		vPTB	
		HR	95%CI	HR	95%CI	HR	95%CI
$PM_{2.5}$	Trimester 1	0.881	0.692–1.120	0.894	0.702–1.137	1.256	0.686–2.300
	Trimester 2	1.251	0.971–1.612	1.292	1.017–1.641	1.363	0.780–2.381
	Trimester 3	0.906	0.711–1.153	0.851	0.676–1.071	0.976	0.711–1.338
	Entire pregnancy	0.998	0.566–1.761	0.982	0.580–1.663	1.671	0.423–6.596
PM_{10}	Trimester 1	0.778	0.658–0.920	0.791	0.669–0.936	0.918	0.566–1.488
	Trimester 2	1.302	1.094–1.549	1.344	1.157–1.561	1.535	0.752–3.133
	Trimester 3	1.051	0.870–1.268	0.987	0.830–1.174	1.156	0.942–1.419
	Entire pregnancy	1.064	0.707–1.602	1.049	0.729–1.509	1.629	0.469–5.664
NO_2	Trimester 1	0.692	0.575–0.834	0.728	0.605–0.876	0.834	0.486–1.429
	Trimester 2	1.512	1.223–1.869	1.512	1.195–1.913	2.493	1.558–3.990
	Trimester 3	1.106	0.979–1.249	1.029	0.925–1.145	1.349	1.217–1.496
	Entire pregnancy	1.158	0.975–1.376	1.133	0.969–1.326	2.805	2.037–3.861
SO_2	Trimester 1	1.058	0.843–1.328	1.064	0.853–1.326	0.942	0.553–1.604
	Trimester 2	0.938	0.822–1.072	0.948	0.824–1.092	0.894	0.710–1.126
	Trimester 3	0.975	0.876–1.085	0.966	0.871–1.072	0.968	0.816–1.147
	Entire pregnancy	0.968	0.812–1.155	0.975	0.840–1.132	0.815	0.455–1.458
O_3	Trimester 1	1.097	0.926–1.299	1.081	0.906–1.288	0.523	0.254–1.075
	Trimester 2	1.027	0.768–1.374	1.108	0.845–1.454	0.915	0.524–1.596
	Trimester 3	1.164	0.980–1.382	1.145	0.984–1.333	0.997	0.683–1.454
	Entire pregnancy	1.311	0.748–2.300	1.371	0.805–2.336	0.477	0.115–1.971

HRs and 95%CIs were calculated for per IQR increment (27 μg/m^3 for $PM_{2.5}$; 37 μg/m^3 for PM_{10}, 29 μg/m^3 for NO_2, and 90 μg/m^3 for O_3) during the study period (2014–2017); all models adjusted for maternal age, parity, year of birth, season of conception (spring: March–May; summer: June–August; fall: September–November; winter: December–February), medical conditions during pregnancy, infant gender, and delivery method; mean ambient temperature during the entire pregnancy was included with natural cubic splines of 3 dfs; districts were fitted as a random effect.

part of the third trimester. When we estimated cumulative effects for three trimesters and the entire pregnancy as most previous studies did, we found $PM_{2.5}$, PM_{10} and NO_2 exposure during the second trimester were associated with the risk of PTB, but we failed to observe a significant association between O_3 and PTB. It could be due to that its window of susceptibility (the 23rd–31st weeks) was relatively shorter and crossed the second and the third trimester.

Few epidemiological studies have assessed the weekly-specific association between air pollution and PTB (Chang et al., 2015; Schifano et al., 2016; Symanski et al., 2016; Warren et al., 2012). Our findings were consistent with two of them. Schifano et al. (Schifano et al., 2016) found the strongest association of PTB with PM_{10}, NO_2 and O_3 exposure in the 22nd–26th gestational weeks, and then significant HRs of PTB decreased with gestational week until the 36th week. Symanski et al. (Symanski et al., 2016) found O_3 exposure in the 17th–28th weeks was associated with PTB of 33–36 completed weeks, and exposure in the 17th–20th and the 25th–28th weeks was associated with PTB of 29–32 completed weeks. Another two studies (Chang et al., 2015; Warren et al., 2012) found that the critical exposure window for $PM_{2.5}$ and PTB was in early and middle pregnancy, which our findings are somewhat, but not fully, consistent with.

Although the underlying mechanisms are currently unclear, recent evidence supports a potential link of critical exposure windows to PTB risk. A recent animal study observed the highest risk of PTB associated with exposure to concentrated ambient $PM_{2.5}$ during a period that aligns with the second and third trimester of human pregnancy (Blum et al., 2017). Both animal and human studies have shown that umbilical artery diameter, blood-flow velocity, and blood-flow volume increase start from the second trimester and continue increasing with advancing gestation to meet fetal increasing demands for oxygen and nutrients (Mayer and Joseph, 2013). These increases also elevate fetal exposure to other endogenous and exogenous factors such as air pollutants and maternal systemic inflammatory mediators (Blum et al., 2017; Wu et al., 2018).

Among all singleton live births, we observed a small inverse association between PM_{10} and NO_2 exposure during early pregnancy and PTB. By excluding Cesarean births and the births with medical conditions during pregnancy, these inverse associations were attenuated, while the positive association between $PM_{2.5}$ exposure during the early pregnancy and PTB was observed. As medical conditions during pregnancy are likely related to medically indicated PTB and are more likely to result in Cesarean births, the observed results might suggest different effects of air pollution exposure on spontaneous and medically indicated PTB, as some previous studies reported (Lee et al., 2013; Zhao et al., 2015). To the best of our knowledge, no published study has investigated critical exposure windows of spontaneous and medically indicated PTB, respectively.

By excluding the births with maternal medical conditions during pregnancy, the effects of NO_2 and O_3 were generally attenuated. This is probably due to the effect modification of maternal comorbidities. Stronger association between pregnancy exposure to NO_2 and PTB has been observed among those with chronic diabetes (Lee et al., 2013), while maternal chronic diabetes, asthma status, or gestational diabetes mellitus strengthened the effects of O_3 exposure on PTB (Lee et al., 2013; Lin et al., 2015). We also noticed the association of each air pollutant exposure during the late pregnancy and PTB became fluctuant, with inverse associations being observed for several weeks. We do not anticipate increases in air pollution exposure biologically confer protection. Chance findings could not be ruled out.

A recent systematic review (Jacobs et al., 2017) indicated that previous studies in China consistently reported SO_2 exposure was associated with PTB. However, our study did not find any obvious association between SO_2 and PTB. This could be due to the relatively low SO_2 level in our study. For example, mean concentrations of SO_2 across the previous studies was 61 μg/m^3 (ranged from 17 μg/m^3 to 182 μg/m^3) (Jacobs et al., 2017), versus 13.2 μg/m^3 in our study. SO_2 emission control has been strictly implemented in China since 2000 (Zhang et al., 2015), and SO_2 levels have mostly decreased in recent years (Wang et al., 2014).

Very few studies have investigated the association between air pollution and PTB subtypes. Several studies suggested a stronger association of very PTB with exposure to $PM_{2.5}$ (Chang et al., 2015; Wu et al., 2009), PM_{10} (van den Hooven et al., 2012; Zhao et al., 2015), and NO_X (Wu et al., 2009). We consistently observed stronger effects of

exposure to $PM_{2.5}$, PM_{10}, and NO_2 on very PTB.

To the best of our knowledge, this is the first study in China assessing impacts of weekly-specific maternal exposure to ambient air pollution on PTB. Our findings add important evidence to the current understanding in susceptible exposure window of air pollution and adverse birth outcomes.

Several limitations should be considered when interpreting the study results. Exposure misclassification could be present due to the lack of information on the exact residential address (as opposed to the district, which was available and used), maternal activity patterns and residential mobility during pregnancy. However, the exposure misclassification is more likely to be non-differential, resulting in attenuation of the associations (Wang et al., 2018a). Chemical compositions of $PM_{2.5}$ and PM_{10} could vary from district to district and might cause different health impacts. Future studies are warranted to further elucidate the association by examining the chemical compositions. In addition, several potential risk factors of PTB, including the presence of cervicovaginal or intrauterine infections, socio-economic status, maternal exercise, smoking (including active smoking and environmental tobacco smoke), and nutritional status were not available, therefore we were unable to control these factors in our models. Earlier studies reported similar effect estimates with and without control for these factors (Brauer et al., 2008; Kim et al., 2007). For example, Kim et al. (Kim et al., 2007) found lower parental education level and higher maternal body mass index were involved in increasing PTB risk, however, the odds ratios and the 95% confidence intervals of PTB associated with PM_{10} exposure during three trimesters changed little with and without adjustment for the above risk factors.

5. Conclusions

Our study found that maternal exposure to $PM_{2.5}$, PM_{10}, NO_2, and O_3 was associated with increased risk of PTB, including overall, moderate, and very PTB. A consistent susceptible exposure window, from middle to late pregnancy (18 to 31 gestational weeks), was observed for each pollutant. The observed associations with $PM_{2.5}$, PM_{10}, and NO_2 exposure were stronger for very PTB. The findings from our study warrant replication in different populations. Further mechanistic study is needed to understand the mechanisms.

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Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.09.021.

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