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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 $\mu g/m^3$) 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 $\mu g/m^3$; HR = 1.048, 95% CI:1.034–1.062), the 26th week for NO_2 (IQR = 29.0 $\mu g/m^3$; HR = 1.060, 95% CI:1.028–1.094), and in the 28th week for O_3 (IQR = 90.0 $\mu g/m^3$; 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