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A Time Series Analysis of Outdoor Air Pollution and Preterm Birth in Shanghai, China

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Objective To investigate the relation between air pollution exposure and preterm birth in Shanghai, China. **Methods** We examined the effect of ambient air pollution on preterm birth using time-series approach in Shanghai in 2004. This method can eliminate potential confounding by individual risk factors that do not change over a short period of time. Daily numbers of preterm births were obtained from the live birth database maintained by Shanghai Municipal Center of Disease Control and Prevention. We used the generalized additive model (GAM) with penalized splines to analyze the relation between preterm birth, air pollution, and covariates. **Results** We observed a significant effect of outdoor air pollution only with 8-week exposure before preterm births. An increase of 10 μg/m^3 of 8-week average PM_{10}, SO_2, NO_2, and O_3 corresponded to 4.42% (95%CI 1.60%, 7.25%), 11.89% (95%CI 6.69%, 17.09%), 5.43% (95%CI 1.78%, 9.08%), and 4.63% (95%CI 0.35%, 8.91%) increase of preterm birth. We did not find any significant acute effect of outdoor air pollution on preterm birth in the week before birth. **Conclusion** Ambient air pollution may contribute to the risk of preterm birth in Shanghai. Our analyses also strengthen the rationale for further limiting air pollution level in the city.

Key words: Air pollution; Preterm birth; Time series

INTRODUCTION

There is substantial evidence that ambient air pollution affects human health[1]. Most studies focus on cardiorespiratory mortality and morbidity[2-3]. Until recently, some studies have started to examine the potential effect of ambient air pollution on pregnancy outcomes[4-13].

Preterm birth is strongly associated with infant mortality and morbidity[14-17]. The etiology of preterm birth is complex but not yet well understood. Few than half of preterm births in developed countries can be attributed to known risk factors[18-19]. However, the role of environmental exposure, such as air pollution, in preterm delivery is not well known. Historically, the first "modern" investigation of the possible influence of air pollution on preterm birth was conducted in Beijing, China by Xu *et al*.[20], who studied the association between maternal exposure to air pollution and preterm delivery in a prospective cohort. They have found a significant reduction in the duration of gestation with increasing levels of sulfur dioxide (SO_2) and total suspended particle (TSP). Results from similar studies in the United States, the Czech Republic, Great Britain, and Brazil have subsequently been reported[11, 21-25]. However, the interpretation of the studies of preterm birth is complicated by the issue of multiple comparisons, and the inconsistency of the results in term of the role of individual pollutants and the timing of exposure[26]. Current evidence is not yet sufficient to infer causality between air pollution and preterm birth, and more studies are warranted.

We studied the associations between preterm delivery and average concentrations of ambient air pollutants (PM_{10}, SO_2, NO_2, and O_3) during the 4, 6, and 8 weeks preceding birth in Shanghai, China. We also examined the possible acute effect of these

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pollutants by narrowing the exposure window to a 1-day interval before birth, with daily lags ranging from 0 to 6 days.

MATERIALS AND METHODS

Data

All live births were obtained from the live birth database maintained by Shanghai Municipal Center of Disease Control and Prevention. Gestational age was computed as the number of weeks between the date of the last menstrual period (LMP) and the date of birth. For birth records missing the date of the LMP, the clinical estimate of gestation was used. Eligible births with gestational ages <37 weeks were considered preterm. The number of preterm births was tallied for each day in 2004.

Daily air pollution data in 2004, including those of particulate matter less than or equal to 10 microns (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3), were collected from Shanghai Environmental Monitoring Center. The daily concentrations for each pollutant were averaged from the available monitoring results of six fixed-site stations under China National Quality Control located in the urban areas of Shanghai. We collected the 24-hour average concentrations for PM_{10}, SO_2, NO_2 and 8-hour (from 10 AM to 6 PM) average concentration for O_3. The 8-hour was used because it is the average time recommended by the World Health Organization for reflecting the most health-relevant exposure to ozone. For the calculation of 24-hour average concentration of PM_{10}, SO_2, and NO_2, it is required to have at least 75% of the one-hour values on that particular day. For the 8-hour average of O_3, at least six hourly values from 10 AM to 6 PM have to be available. If a station had more than 25% of the values missing for the whole period of analysis, the entire station was excluded from the analysis.

To allow adjustment for the possible effect of weather on preterm birth, daily average temperature and humidity data were collected from Shanghai Meteorological Bureau. The weather data were measured at a fix-site station located in Xuhui District of Shanghai.

Statistical Methods

We used the generalized additive model (GAM) with penalized splines to analyze the preterm birth, air pollution, and covariates. Because the number of preterm births was small and typically followed a Poisson distribution[24], the core analysis was a generalized additive model (GAM) with log link and Poisson error that accounted for smooth fluctuations in daily number of preterm births.

We first built the basic models for daily numbers of preterm births which did not include the air pollution variables. We incorporated smoothed spline functions of time and weather conditions, which can accommodate non-linear and non-monotonic patterns between preterm birth and time/weather conditions, offering a flexible modeling tool[27]. Other covariates, such as day of the week (DOW), were also included in the basic models. Residuals of each model were examined to check whether there were discernible patterns and autocorrelation by means of residual plots and partial autocorrelation function plots, respectively.

After the establishment of basic models, we introduced the pollutant variables into the models and analyzed their effects on preterm births. The number of gestations at risk for preterm birth was used as an offset. Generalized cross-validation (GCV) scores were used to compare the relative quality of the mortality predictions across these non-nested models and how well the models fit the data[27].

Previous study has reported that both acute (up to 7 days) and subchronic (6 weeks) exposures to air pollution are associated with an increase of preterm births[24]. In our analysis, we adopted two settings of lag structure for exposure assessment. We used daily pollutant levels to compute the mean air pollution concentration value for the 4, 6, and 8-week periods proceeding each day of observation. For the analysis of the acute effect of air pollution, we also investigated risk for preterm birth in relation to levels of pollutants for a single-day exposure window with lags from 0 to 6 days before birth.

All analyses were conducted by R 2.1.1 using MGCV package. The results are presented as the percent change in daily preterm births per 10 $\mu g/m^3$ increase of air pollutant concentrations.

RESULTS

Descriptive Statistics

A total of 3346 preterm births occurred over the entire study period. The number of preterm births ranged from 1 to 21 per day, with a mean of approximately 9.1 per day and a median of 9.0 per day. The mean concentrations of PM_{10}, SO_2, NO_2, and O_3 were 101.3 $\mu g/m^3$, 55.7 $\mu g/m^3$, 70.6 $\mu g/m^3$, and 251.3 $\mu g/m^3$, respectively.

Mean 4, 6, and 8-week Exposure Models

Table 2 displays estimates of the association of

TABLE 1

Descriptive Statistics for Daily Number of Preterm Births and Air Pollutant Concentrations

	$\bar{x} \pm s$	Min	*P* (25)	Median	*P* (75)	Max
Daily Number of Preterm Births and Air Pollutants Concentrations	9.1±0.2	1.0	7.0	9.0	11.0	21.0
PM_{10} (μg/m^3)	101.3±3.0	22.0	59.4	83.0	130.1	332.5
SO_2 (μg/m^3)	55.7±1.4	11.3	35.5	51.5	71.2	163.2
NO_2 (μg/m^3)	70.6±1.4	16.5	51.5	67.3	84.0	168.5
O_3 (μg/m^3)	65.3±2.1	5.3	37.8	56.2	86.8	251.3

mean 4, 6, and 8-week air pollution exposure and risk for preterm delivery. Basically, we observed a significant effect of outdoor air pollution only with 8-week exposure before preterm births. An increase of 10 μg/m^3 of 8-week average PM_{10}, SO_2, NO_2, and O_3 corresponded to 4.42% (95%CI 1.60%, 7.25%), 11.89% (95%CI 6.69%, 17.09%), 5.43% (95%CI 1.78%, 9.08%), and 4.63% (95%CI 0.35%, 8.91%) increase of preterm births.

Acute Effect (Daily) Exposure Models

Among the 1-day acute time windows examined, preterm birth was not significantly associated with outdoor air pollution in any lag day we considered (Fig. 1).

TABLE 2

Percent Increase for Preterm Birth With Exposure to Outdoor Air Pollutants in 4, 6, and 8 Weeks Preceding Birth in Shanghai

		Mean	95% CI
PM_{10}	4 Weeks	-0.20	-2.23, 1.83
	6 Weeks	-0.94	-3.38, 1.49
	8 Weeks*	4.42	1.60, 7.25
SO_2	4 Weeks	2.44	-1.01, 5.89
	6 Weeks	0.90	-3.26, 5.06
	8 Weeks*	11.89	6.69, 17.09
NO_2	4 Weeks	-0.60	-3.62, 2.42
	6 Weeks	-1.97	-5.37, 1.43
	8 Weeks*	5.43	1.78, 9.08
O_3	4 Weeks*	3.08	0.15, 6.01
	6 Weeks	2.96	-0.59, 6.52
	8 Weeks*	4.63	0.35, 8.91

Note. *With statistically significant difference (P<0.05).

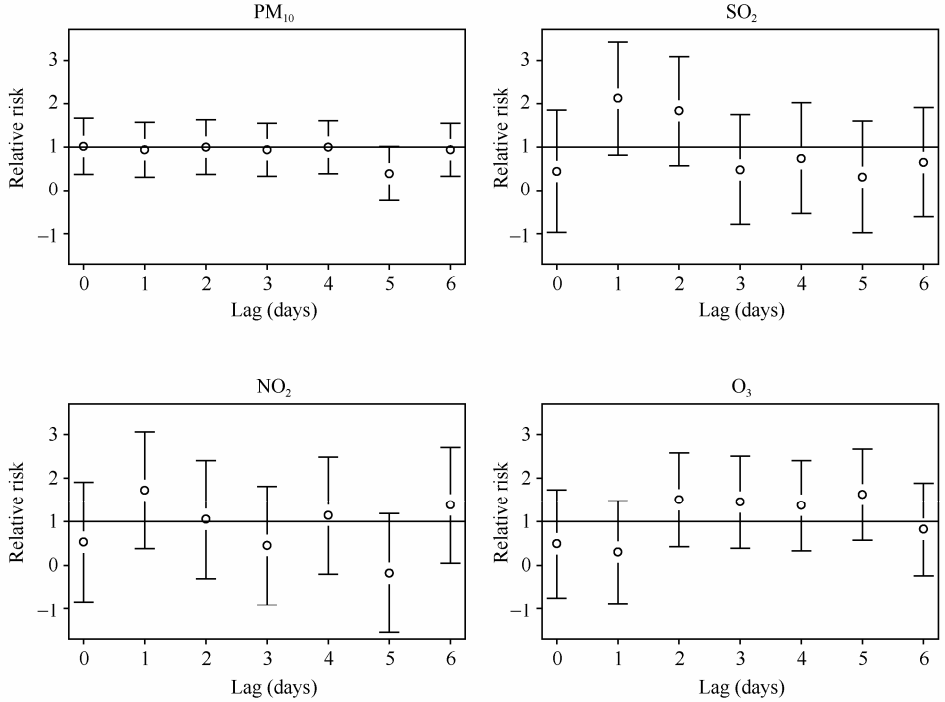

FIG. 1. Relative risks and 95% CIs for preterm birth per 10 μg/m^3 increase in PM_{10}, SO_2, NO_2, and O_3, lagged 0-6 days before birth.

DISCUSSION

Evidence gained in this study showed that the current level of outdoor air pollution in Shanghai is associated with preterm birth. Specifically, we observed an increased risk only during the last 8 weeks of pregnancy with exposure to outdoor air pollutants ($PM_{10}/SO_2/NO_2/O_3$), suggesting a sub-chronic accumulating role of air pollution in preterm birth. The magnitude of our finding is comparable to previous study conducted in the US[24]. We did not find any significant acute effect of outdoor air pollution on preterm birth in the week before birth.

With regard to the relation between air pollution and preterm delivery, most previous studies relied on spatial analyses comparing high-exposure areas with low-exposure areas. Therefore, a potential limitation of these previous studies is inadequate control for confounding by individual risk factors. In addition, birth record data do not include information on all risk factors that could potentially confound the relationship between air pollution and preterm delivery. Time-series design, according to its definition, could be used to investigate the effect of air pollution without the influence of known and unknown individual risk factors that do not vary over short periods of time. Actually, time-series methods have been successfully used for assessment of short-term health effects of air pollution on cardio-respiratory mortality and morbidity outcomes[28]. Although limitations arise from ecologic study design (ecologic fallacy) and the "harvesting" (mortality displacement) effect[29], time-series methods are more powerful and better able to characterize the population exposure effects than those based on geographic aggregations in cross-sectional studies. To our knowledge, only one study has looked at the effect of air pollution on preterm delivery using a time-series design with exposure contrasts over time rather than space[24]. The time-series approach we employed here can remove the influence of covariates that vary across individuals but not within individuals over a short period of time.

Air pollution exposure and associated adverse birth effects could be considered for the following reasons. Firstly, air pollution may affect DNA and its transcription. DNA adducts have been observed in areas with high exposure of pollution, with placental DNA adducts more common among mothers exposed to high level of air pollution[30]. There may be a link between DNA adducts and fetal growth as newborns with more adducts have lower birth weight and length[31]. Secondly, the potential mechanisms could be related with hematologic factors. Changes in blood viscosity due to inflammation as a result of exposure to PM and SO_2 have been observed[32]. Inflammation is also related to preterm delivery and inadequate placental perfusion[33-34]. Another possible pathway is a more long-term process that involves maternal infection during pregnancy. Although air pollution does not directly cause maternal infections, exposure to specific pollutants may impair immune function, which could enhance susceptibility to infection[35-36]. Subtle changes in the immune system could result in changes among vaginal flora, which promote vaginal pathogens associated with bacterial vaginosis, a risk factor for preterm birth[37]. Studies have also shown associations between preterm labor and delivery and systemic maternal infections, such as pneumonia and pyelonephritis, as well as local infections, such as intra-amniotic and urinary infections[38-41]. This pathway could explain the associations observed in this study for air pollution in the 8 weeks before birth. So far, although the specific steps of these pathways need to be further clarified, the similarity of effects of air pollution to those of smoking[42-43] supports the biologic plausibility of the effects.

Our study area including nine urban districts of Shanghai, is densely populated. Within an area of 279 square kilometers, there are around seven-million permanent residents and six monitoring stations with National Quality Control providing the exposure data for this study. In addition, compared with the residents in the developed countries, a relatively lower proportion of Shanghai residents has access to air conditioning. Thus, the monitored ambient air pollution data might have been more closely associated with average population exposures in Shanghai than in other study locations of developed countries. Of course, the limitations of our exposure assessment should also be noted. As in most previous time-series studies, we used the simply averaged monitoring results across various stations as the proxy of population exposure level to air pollution. That assignment method may raise a number of issues, such as the variance of pollutant measurements differing from monitoring location to monitoring location, and the difference between ambient monitoring results and personal exposure level to air pollution. How to remove these influences challenges the accurateness of our exposure assessment and the following time-series analysis. The resulting measurement error may have substantial implication for interpreting the time-series air pollution studies[44], although a study suggested that this measurement error would generally tend to bias estimates downward[45].

In summary, our data from Shanghai confirm

previous reports about the adverse effect of ambient air pollution. Currently, since many people live in urban centers and are chronically exposed to high levels of air pollution, the public health impact could be considerable. Additional studies in other geographical areas and time periods would be warranted. Further research needs to be conducted with more detailed information on personal exposure, effect modifiers, and other adverse pregnancy outcomes.

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