Environmental Science and Pollution Research (2022) 29:67380–67389
https://doi.org/10.1007/s11356-022-20379-8

RESEARCH ARTICLE

The acute effect and lag effect analysis between exposures to ambient air pollutants and spontaneous abortion: a case-crossover study in China, 2017–2019

Wenzheng Zhou[1] · Xin Ming[1] · Qing Chen[2] · Xiaoli Liu[1] · Ping Yin[3]

Received: 24 December 2021 / Accepted: 18 April 2022 / Published online: 6 May 2022

Abstract

Introduction Recent studies demonstrated that living in areas with high ambient air pollution may have adverse effects on pregnancy outcomes, but few studies have investigated its association with spontaneous abortion. Further investigation is needed to explore the acute effect and lag effect of air pollutants exposure on spontaneous abortion.

Objective To investigate the acute effect and lag effect between exposure to ambient air pollutants and spontaneous abortion.

Methods Research data of spontaneous abortion were collected from the Chongqing Health Center for Women and Children (CQHCWC) in China. The daily ambient air pollution exposure measurements were estimated for each woman using inverse distance weighting from monitoring stations. A time-stratified, case-crossover design combined with distributed lag linear models was applied to assess the associations between spontaneous pregnancy loss and exposure to each of the air pollutants over lags 0–7 days, adjusted for temperature and relative humidity.

Results A total of 1399 women who experienced spontaneous pregnancy loss events from November 1, 2016, to September 30, 2019, were selected for this study. Maternal exposure to particulate matter 2.5 ($PM_{2.5}$), particle matter 10 (PM_{10}) nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) exhibited a significant association with spontaneous abortion. For every 20 μg/m^3 increase in $PM_{2.5}$, PM_{10}, NO_2, and SO_2, the RRs were 1.18 (95% *CI*: 1.06, 1.34), 1.12 (95% *CI*, 1.04–1.20), 1.15 (95% *CI*: 1.02, 1.30), and 1.92 (95% *CI*: 1.18, 3.11) on lag day 3, lag day 3, lag day 0, and lag day 3, respectively. In two-pollutant model combined with $PM_{2.5}$ and PM_{10}, a statistically significant increase in spontaneous abortion incidence of 18.0% (*RR* = 1.18, 95% *CI*: 1.06, 1.32) was found for a 20 μg/m^3 increase in $PM_{2.5}$ exposure, and 11.2% (*RR* = 1.11, 95% *CI*: 1.03, 1.20) for a 20 μg/m^3 increase in PM_{10} exposure on lag day 3, similar to single-pollutant model analysis.

Conclusion Maternal exposure to high levels of $PM_{2.5}$, PM_{10}, NO_2, and SO_2 during pregnancy may increase the risk of spontaneous abortion for acute effects and lag effects. Further research to explore sensitive exposure time windows is needed.

Keywords Air pollution · Exposure · Spontaneous abortion · Case-crossover

Responsible Editor: Lotfi Aleya

Highlights

1. The risk of spontaneous abortion caused by exposure to air pollutants is attracted attention.
2. Chongqing's special air quality changes provide a unique research environment different from that of Occident.
3. A time-stratified, case-crossover design and distributed lag linear models were applied.
4. Maternal exposure to high levels of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 may increase the risk of spontaneous abortion.

✉ Xiaoli Liu
liuxiaolicqfy@163.com

Extended author information available on the last page of the article

Abbreviations

$PM_{2.5}$	Particulate matter 2.5
PM_{10}	Particulate 10
SO_2	Sulfur dioxide
NO_2	Nitrogen dioxide
CO	Carbon monoxide
O_3	Ozone
DLM	Distributed lag linear model
CQHCWC	Chongqing Health Center for Women and Children
RR	Relative risk
CI	Confidence interval
SD	Standard deviation

Introduction

Nowadays, many studies have reported that ambient air pollution exposure is related to adverse pregnancy outcomes (Chen et al. 2021; Guo et al. 2019a; Zhu et al. 2015), including preterm birth (Li et al. 2017), low birth weight, stillbirth (Bekkar et al. 2020), and abortion (Enkhmaa et al. 2014b). But few studies have investigated the association between maternal exposure to ambient air pollution and spontaneous abortion (Di Ciaula and Bilancia 2015b; Moridi et al. 2014). Spontaneous abortion, also called spontaneous pregnancy loss, was defined as a subsequent negative urine pregnancy test after a positive test, a clinically confirmed pregnancy loss, or onset of menstruation depending on gestational age (Dastoorpoor et al. 2018). Recent literature has demonstrated that air pollutants exposure increases the risk of spontaneous abortion, but the results vary by pollutants and demographic factors (Ha and Mendola 2019; Moridi et al. 2014). The sensitive time window of exposure remains inconsistent in different studies. Further research is still essential to explore the effect of air pollutants exposure on spontaneous abortion, especially the lag effect and acute effect.

There is a lot of literature related to air pollutants exposure and pregnancy outcomes in China (Fang et al. 2020; Guo et al. 2019b; Zhang et al. 2016), but the association between exposure to ambient air pollutants and spontaneous abortion is still rarely reported. Chongqing is the largest municipality in China, with a permanent population of 31 million, an industrial city located along the Yangtze River with 40 districts. Compared with other cities in China, Chongqing formerly has poor air quality, known as the famous "Fog City." The air quality of Chongqing has been improving since 2014 through the gradually strengthened management by the local government. Chongqing's air quality has greatly improved in 2019 according to the monitoring indicators.

The special air quality changes in Chongqing city provide a unique research environment different from European and American countries and also give us a peculiar sample to study the effect of air pollution exposure on spontaneous abortion.

Therefore, we conducted the study with a large sample size and precise individual exposure assessment to explore the risk of spontaneous abortion with exposure to air pollutants in a special Chinese city. It focused on the purpose to assess the lag effect and acute effect and to estimate the individual and combined effects of air pollutants.

Materials and methods

Study population

Research data about the cases of spontaneous abortion were collected from the Chongqing Health Center for Women and Children (CQHCWC), which is the biggest maternity referral hospital in Chongqing. It received hospitalized patients with spontaneous abortion across the whole of Chongqing city, providing us with large-scale and widely distributed cases for research. The cases of spontaneous abortion were identified in CQHCWC using the following diagnosis codes: ICD-10 — O03.300×061, O03.4-O03.9 (Leiser et al. 2019). All the research women were diagnosed as spontaneous abortion or incomplete spontaneous abortion, with or without complications. A total of 1794 spontaneous abortion cases in the medical record room of CQHCWC from 2017 to 2019 were collected. Women over the age of 35 years old are more likely to suffer pregnancy loss because old age is a severe risk factor for spontaneous abortion (DeVilbiss et al. 2020; Eroglu et al. 2020; Sileo et al.). To avoid interference, this study has eliminated them. The cases whose gestational age was unknown and the fertilization time cannot be estimated were excluded. The events that occurred to women residing outside Chongqing at fertilization time were excluded. For women who experienced two or more than two pregnancy abortion events, only the first event if the two occurred within 14 weeks was included. Because whether a second observation was truly another independent pregnancy loss event or related to the first event was unable to verify. Finally, the sample consisted of 1399 spontaneous abortion events that were selected for the final analysis after a series of exclusion criteria. This study was approved by the institutional ethical committee board of CHCWC.

Air pollution exposure and other covariate data

Air pollution concentration data, including $PM_{2.5}$, PM_{10}, SO_2, carbon monoxide (CO), NO_2, and ozone (O_3), were measured at the air monitoring stations for the period from January 1, 2016, to December 30, 2019, in 9 main districts of Chongqing, China. The air pollution data was all collected from the Chinese national urban air quality monitoring platform published by the China National Environmental Monitoring Station of the Ministry of Ecology and Environment (http://www.zhb.gov.cn). The data of O_3 and CO was incomplete, so only $PM_{2.5}$, PM_{10}, NO_2, and SO_2 were analyzed in this study. The exposure time of acute-effect in this study was estimated at the fertilization time, which was calculated according to the time of the last menstruation of every woman (Leiser et al. 2019).

Based on the detailed residence address of every research woman and the location of air monitoring stations, we got each latitude and longitude through the Amap open platform (https://lbs.amap.com/). Then according to their exact spatial locations in the digital map, we calculated the distance between each woman's residence and monitoring sites by using ArcGIS (version 10.2). Daily ambient air pollution exposure measurements were estimated for each woman by inverse distance weighting of all observations from monitoring stations (Leiser et al. 2019). The benefit was that we were able to assign exposure values at an individual level, rather than distinct-level measurements from the raw data.

The weather data was collected from the National Weather Data Sharing System (http://data.cma.cn/). Daily mean temperature (°C) and relative humidity (%) were used for analysis. All analyses were controlled for confounding factors, such as daily average temperature, age (years), previous pregnancy history (yes or no), and race/ethnicity. Daily exposure measurements were calculated as the average concentrations of the day of all the spontaneous abortion cases and the preceding lags 0–7 days of air pollutants (Leiser et al. 2019).

Statistical analysis

A case-crossover study was designed for analyzing the association between short-term air pollution exposure and the risk of spontaneous pregnancy loss. This kind of design has been widely used in similar research fields, characterized by selecting a case or event date as her own control (Janes et al. 2005). Time-stratified referent selection was applied because it can control for the season, month, and day of the week. The same days of the other week in the same month for the event day of each individual were chosen as referent days. For example, if the conception day of an object was Monday, the referent days were another several Monday in the same month. Then there were three or four referent periods per event day. This design increased efficiency, avoided overlap bias and time-trend bias, and matched on time-dependent confounders.

Relative risks (RRs) and 95% confidence intervals (CIs) for a 20 μg/m^3 increase in $PM_{2.5}$, PM_{10}, SO_2, and NO_2 exposures were calculated. Spearman's correlation coefficients were used to evaluate the associations between each pair of air pollutants. The associations between air pollution and spontaneous abortion were estimated by using the generalized linear model and distributed lag linear model (DLM) (Ananth et al. 2018; Leiser et al. 2019). To take into account possible over-dispersion of daily spontaneous abortion counts, we used quasi-Poisson estimation. We used R version 3.4.2 with "dlnm" package (version 2.1.3) for data statistical analysis (Ananth et al. 2018). All statistical tests were two-sided. A probability value of <0.05 was considered statistical significance.

Result

Descriptive statistics of women and ambient air pollutants

The 1399 research women in the study ranged in age from 18 to 35 years old, with an average age of 28 years old. Among them, 35.7% of women had not been pregnant before, 29.4% had a previous pregnancy, and 34.9% had two or more pregnancies. More than two thirds (72.1%) of women had never given birth before. The mean (standard deviation) abortion gestational age was 11.3 (3.5) weeks.

The descriptive statistics for ambient air pollutants $PM_{2.5}$, PM_{10}, SO_2, NO_2, average temperature, and relative humidity at lag day 0 for spontaneous abortion case days were displayed (Table 1). The mean concentration and their corresponding ranges (min–max) were 33.61 μg/m^3 (7.96–177.91 μg/m^3) for $PM_{2.5}$, 65.76 μg/m^3 (11.85–241.14 μg/m^3) for PM_{10}, 43.31 μg/m^3 (15.08–89.81 μg/m^3) for NO_2, 9.32 μg/m^3 (3.35–33.96 μg/m^3) for SO_2, 19.33 ℃ (4.50–36.50 ℃) for apparent mean temperature and 75.26% RH (37.00–97.00% RH)

Table 1 Descriptive statistics for ambient air pollutants

Pollutants	Mean	SD	Median	Minimum	Maximum	Range	Skew	Kurtosis
$PM_{2.5}$ (μg/m^3)	41.1	26.58	33.61	7.96	177.91	169.95	1.81	3.89
PM_{10} (μg/m^3)	65.76	36.16	57.53	11.85	241.14	229.29	1.47	2.76
NO_2 (μg/m^3)	43.31	13.33	41.59	15.08	89.81	30.62	1.41	3.32
SO_2 (μg/m^3)	9.32	4.06	8.41	3.35	33.98	30.62	1.41	3.32
Temperature (℃)	19.33	7.91	19.10	4.50	36.50	32.00	0.16	−1.06
Humidity (%RH)	75.26	11.44	77.00	37.00	97.00	60.00	−0.58	−0.19

Abbreviations: *SD*, standard deviation. Note: Average concentrations of pollutants from inverse distance weighting of all observations (1399 women) from monitoring stations, Chongqing, China, November 1, 2016 to September 30, 2019 during the entire study period. All pollutant correlations were positive. Correlations between air pollutants and meteorological factors were mostly negative, except for $PM_{2.5}$ and humidity. A positive correlation between $PM_{2.5}$ and PM_{10} ($r = 0.957$), and a negative correlation between $PM_{2.5}$ and average daily temperature ($r = -0.493$) were observed (Table 2).

Concentration changes of ambient air pollutants for women

Figure 1 shows the daily concentration variation trend of $PM_{2.5}$, PM_{10}, SO_2, and NO_2 of the 1399 women from 2016 to 2019 (the time of fertilization was calculated by the time of last menstruation, so the exposure time moved forward as a whole). The daily concentration of each ambient air pollutant was the mean value of the concentration of all spontaneous abortion cases on that day (calculated by the inverse distance weighted for each case). The results indicated that the seasonal trend is obvious, and the air quality is gradually improving.

Associations between air pollutants exposure and spontaneous abortion

The relationship between the crude RRs for spontaneous pregnancy loss and the exposure of the gaseous air pollutants for lag effects and acute effects are shown in Table 3. For each 20 μg/m^3 $PM_{2.5}$ increase, the relative risk of spontaneous pregnancy loss increased by 18.4% (*RR* = 1.184, 95% *CI*: 1.06, 1.34) on lag day 3. For every 20 μg/m^3 increase in PM_{10}, NO_2, and SO_2, there were 11.5% (*RR* = 1.115, 95% *CI*: 1.04, 1.20), 14.9% (*RR* = 1.149, 95% *CI*: 1.02, 1.30), and 91.7% (*RR* = 1.917, 95% *CI*: 1.18, 3.11) increase in spontaneous abortion incidence on lag day 3, lag day 0, and lag day 3, respectively. The results of the adjusted model for apparent mean temperature and humidity were consistent with the previous crude model (Table 3).

Results of combined effect analysis of two-pollutant models

The results of combined effect analysis for two-pollutant models are shown in Table 4. After adjusting apparent mean temperature and humidity, the association between two air pollutants and spontaneous abortion was calculated (Ananth et al. 2018). In a two-pollutant model combined with $PM_{2.5}$ and PM_{10}, a statistically significant increase in spontaneous abortion incidence of 18.0% (*RR* = 1.18, 95% *CI*: 1.06, 1.32) was found for a 20 μg/m^3 increase in $PM_{2.5}$ exposure, and 11.2% (*RR* = 1.112, 95% *CI*: 1.03, 1.20) for a 20 μg/m^3 increase in PM_{10} exposure on lag day 3, similar to single-pollutant model analysis. As shown in Table 4, combined with $PM_{2.5}$ and NO_2, there were 18.7% (*RR* = 1.187, 95% *CI*: 1.06, 1.33) and 14.8% (*RR* = 1.148, 95% *CI*: 1.00, 1.31) significant increase in spontaneous abortion incidence on lag day 3 and lag day 0 respectively. Similarly, for $PM_{2.5}$ and SO_2, the RRs were 1.18 (95% *CI*: 1.06, 1.32) and 1.88 (95% *CI*: 1.16, 3.06) both on lag day 3 with statistical significance.

Discussion

This study carried out a time-stratified, case-crossover design with DLM model to evaluate the acute effect of air pollutants exposure on spontaneous abortion at each lag from 0 to 7 days of the calculated fertilization time. In particular, the city with special air quality changes was selected in this study with a larger sample size population. According to the results of this study, it was found that there were crucial associations between ambient air pollutants exposure and spontaneous pregnancy loss. Compared to the current literature, the present study is the largest sample size research on the relationship between ambient air pollutants and spontaneous abortion among the Chinese population. For every 20 μg/m^3 increase in $PM_{2.5}$, PM_{10}, NO_2, and SO_2, the RRs were 1.18 (95% *CI*: 1.06, 1.34), 1.12 (95% *CI*, 1.04–1.20), 1.15 (95% *CI*: 1.02, 1.30), and 1.92 (95% *CI*: 1.18, 3.11) on lag day 3, lag day 3, lag day 0, and lag day 3, respectively ($p < 0.05$).

Table 2 Spearman's correlation coefficients between ambient air pollutants and weather conditions

Pollutants	$PM_{2.5}$	PM_{10}	NO_2	SO_2	Temperature	Humidity
$PM_{2.5}$	1					
PM_{10}	0.957**	1				
NO_2	0.747**	0.807**	1			
SO_2	0.633**	0.721**	0.690 **	1		
Temperature	−0.493**	−0.358**	−0.324**	−0.211**	1	
Humidity	0.044	−0.184**	−0.067*	−0.312**	−0.418**	1

Spearman's correlation coefficients among daily average concentrations of air pollutants and meteorological factors in the study in Chongqing, China, November 1, 2016 to September 30, 2019. **denotes $P < 0.001$; *denotes $P < 0.05$

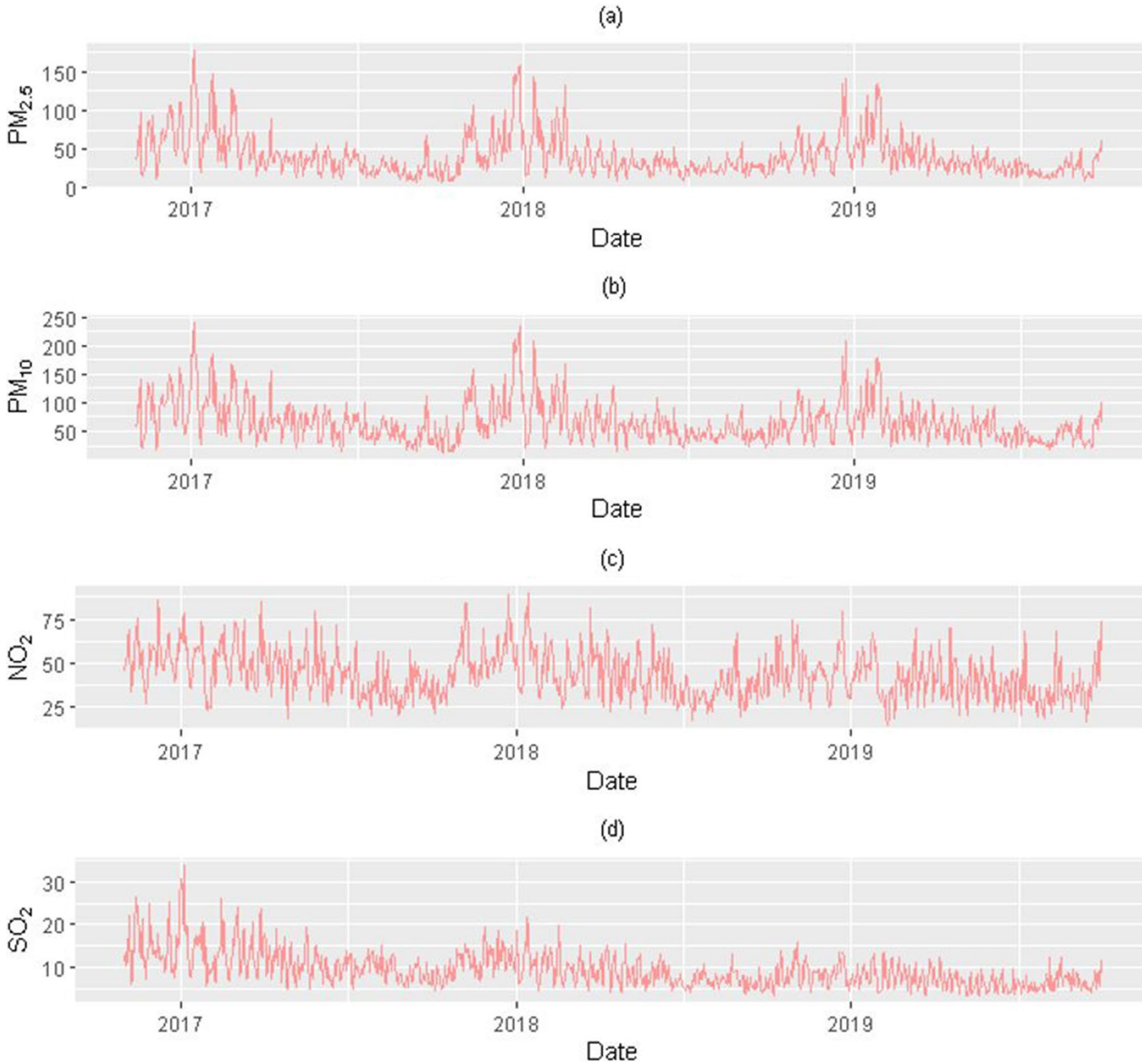

Fig. 1 Daily averages of air pollutants in Chongqing, China, November 1, 2016 to September 30, 2019

The results of single-pollutant model and two-pollutant models adjusted for apparent mean temperature and humidity were similar. Results indicated an increase in the occurrence of spontaneous abortion associated with the exposure to ambient $PM_{2.5}$, PM_{10}, NO_2, and SO_2 because of their acute effect and lag effect (Figure 2).

The findings for $PM_{2.5}$ and other air pollutants are generally consistent with those of existing related studies (Leiser et al. 2019; Liang et al. 2019; Zhang et al. 2019). In the first case-crossover study which investigates whether acute common air pollutants exposure trigger spontaneous pregnancy loss (Leiser et al. 2019), Leiser et al. found that a 10 μg/m^3 increases in the average concentration of NO_2 during a much shorter duration in time (3 days, 7 days) were associated with a 16% increase in the odds of spontaneous pregnancy loss. In a study conducted in China, Xue T and Zhang Q found that fertility rates were significantly decreased by 2.0% (95% *CI*: 1.8%, 2.1%) per 10 μg/m^3 increment of $PM_{2.5}$ (Xue and Zhang 2018). Another study reported a strong correlation between NO_2 and spontaneous pregnancy loss ($r > 0.8$) (Enkhmaa et al. 2014a). In a systematic review by Conforti et al., they found elevated air pollution increased the risk of diminished fertility outcomes for the exposed population, including miscarriage and rates of live births (Conforti et al. 2018). A time-series study by Dastoorpoor et al. indicated a significant relationship between each 10 μg/

Table 3 Crude and adjusted RRs and 95% CIs for spontaneous pregnancy loss and maternal air pollutants exposure

Pollutants	Lag	Crude *RR* (95% *CI*)	*p* value	Adjusted *RR* (95% *CI*)[a]	*p* value
$PM_{2.5}$	lag0	1.182 (0.941, 1.483)	0.196	1.071 (0.986, 1.164)	0.160
	lag1	0.906 (0.809, 1.015)	0.145	0.906 (0.808, 1.015)	0.146
	lag2	1.004 (0.898, 1.121)	0.923	1.004 (0.898, 1.121)	0.923
	lag3	1.184 (1.060, 1.323)	0.034	1.183 (1.059, 1.322)	0.035
	lag4	0.849 (0.757, 0.951)	0.051	0.848 (0.757, 0.951)	0.050
	lag5	0.978 (0.876, 1.091)	0.638	0.976 (0.874, 1.090)	0.614
	lag6	1.084 (0.976, 1.205)	0.183	1.085 (0.976, 1.206)	0.180
	lag7	1.017 (0.941, 1.100)	0.619	1.015 (0.938, 1.099)	0.659
PM_{10}	lag0	1.032 (0.977, 1.090)	0.279	1.033 (0.975, 1.093)	0.283
	lag1	0.954 (0.885, 1.027)	0.245	0.954 (0.885, 1.028)	0.247
	lag2	0.998 (0.928, 1.073)	0.941	0.998 (0.928, 1.073)	0.941
	lag3	1.115 (1.035, 1.200)	0.038	1.114 (1.035, 1.199)	0.038
	lag4	0.908 (0.842, 0.979)	0.058	0.907 (0.842, 0.978)	0.055
	lag5	0.971 (0.904, 1.044)	0.403	0.970 (0.903, 1.043)	0.391
	lag6	1.055 (0.984, 1.131)	0.181	1.055 (0.984, 1.131)	0.181
	lag7	1.017 (0.965, 1.072)	0.491	1.015 (0.963, 1.071)	0.537
NO_2	lag0	1.149 (1.019, 1.295)	0.046	1.152 (1.019, 1.303)	0.048
	lag1	0.909 (0.784, 1.055)	0.240	0.912 (0.785, 1.059)	0.255
	lag2	0.976 (0.841, 1.133)	0.696	0.976 (0.841, 1.134)	0.697
	lag3	1.075 (0.926, 1.247)	0.340	1.073 (0.924, 1.245)	0.350
	lag4	0.947 (0.816, 1.100)	0.445	0.946 (0.814, 1.099)	0.440
	lag5	1.021 (0.879, 1.187)	0.735	1.019 (0.876, 1.186)	0.759
	lag6	0.933 (0.804, 1.083)	0.356	0.931 (0.802, 1.082)	0.346
	lag7	1.087 (0.963, 1.227)	0.217	1.084 (0.960, 1.224)	0.229
SO_2	lag0	0.838 (0.547, 1.285)	0.399	0.822 (0.515, 1.311)	0.394
	lag1	1.039 (0.629, 1.717)	0.844	1.052 (0.637, 1.737)	0.799
	lag2	0.843 (0.511, 1.392)	0.469	0.844 (0.511, 1.392)	0.472
	lag3	1.917 (1.182, 3.111)	0.040	1.913 (1.179, 3.104)	0.041
	lag4	0.681 (0.412, 1.127)	0.183	0.674 (0.407, 1.116)	0.176
	lag5	0.659 (0.400, 1.085)	0.156	0.655 (0.398, 1.079)	0.152
	lag6	1.215 (0.754, 1.959)	0.404	1.209 (0.750, 1.949)	0.414
	lag7	0.979 (0.643, 1.491)	0.894	0.955 (0.626, 1.458)	0.785

RRs were estimates based on per 20 μg/m^3 increase in $PM_{2.5}$, PM_{10}, NO_2, and SO_2. [a]Adjusted for average temperature and relative humidity

m^3 increase in SO_2 and spontaneous abortion in lag 0 and 9 days using a quasi-Poisson distributed lag model (Dastoorpoor et al. 2018).

However, some inconsistencies between our study and previous research should be noticed (Ciaula and Bilancia 2015a; Frutos et al. 2015; Hou et al. 2014). In a study conducted by Moridi et al., findings demonstrated that odd ratios of abortion in the areas with higher concentrations of NO_2 and PM_{10} were 0.96 and 1.01, respectively ($P < 0.05$); there was no significant association between prenatal exposure to SO_2 and abortion (Moridi et al. 2014). Gaskins et al. conducted a case-crossover study with a sample size of 3585 women and found that an increase in PM_{10} (per 3.9 μg/m^3) and $PM_{2.5}$ (per 2.0 μg/m^3) in the year before pregnancy was significantly associated with 1.12 (95% *CI*: 1.06, 1.19) and 1.10 (95% *CI*: 1.04, 1.17) higher odds of spontaneous abortion, respectively (Gaskins et al. 2019). The differences in the research methods and the component of air pollutants in different areas may cause various results (Raz et al. 2018; Wdowiak et al. 2018). This study with a large sample size and precise individual exposure assessment provided more convincing research evidence.

The focus of this study is not only on the associations between air pollutants level and spontaneous abortion with RRs but also on the combined effect of two-pollutant models. Due to the positive correlation between $PM_{2.5}$ and PM_{10} ($r = 0.96$), NO_2 ($r = 0.75$), and SO_2 ($r = 0.63$), the results of two-pollutant models were similar to the univariate analysis. That is consistent with many articles that studied the relationship between ambient air pollutants and birth

Table 4 Percent change in risk (and 95% *CI*) of incidence per 20 μg/m^3 increase in two-pollutant models, adjusted for humidity and apparent mean temperature, Chongqing, China, 2017–2019: Distributed lag linear model

Pollutants	Lag	Adjusted RR (95%CI)	*p* value
$PM_{2.5}$ + PM_{10}			
$PM_{2.5}$	lag0	1.182 (0.941, 1.483)	0.196
	lag1	0.902 (0.805, 1.011)	0.135
	lag2	1.004 (0.899, 1.122)	0.916
	lag3	1.180 (1.057, 1.318)	0.036
	lag4	0.849 (0.757, 0.951)	0.051
	lag5	0.977 (0.875, 1.090)	0.620
	lag6	1.084 (0.976, 1.205)	0.182
	lag7	1.014 (0.937, 1.098)	0.670
PM_{10}	lag0	0.952 (0.817, 1.109)	0.487
	lag1	0.949 (0.880, 1.023)	0.213
	lag2	0.998 (0.928, 1.074)	0.945
	lag3	1.112 (1.032, 1.197)	0.042
	lag4	0.907 (0.842, 0.978)	0.056
	lag5	0.970 (0.902, 1.043)	0.392
	lag6	1.055 (0.984, 1.131)	0.183
	lag7	1.015 (0.963, 1.070)	0.534
$PM_{2.5}$ + NO_2			
$PM_{2.5}$	lag0	1.032 (0.937, 1.137)	0.484
	lag1	0.912 (0.813, 1.022)	0.166
	lag2	1.003 (0.897, 1.120)	0.949
	lag3	1.187 (1.062, 1.326)	0.033
	lag4	0.851 (0.759, 0.954)	0.053
	lag5	0.977 (0.875, 1.091)	0.629
	lag6	1.085 (0.976, 1.206)	0.182
	lag7	1.018 (0.941, 1.102)	0.600
NO_2	lag0	1.148 (1.004, 1.312)	0.012
	lag1	0.910 (0.781, 1.06)	0.043
	lag2	0.976 (0.840, 1.134)	0.696
	lag3	1.072 (0.923, 1.245)	0.356
	lag4	0.946 (0.814, 1.099)	0.438
	lag5	1.019 (0.876, 1.186)	0.753
	lag6	0.931 (0.801, 1.082)	0.347
	lag7	1.084 (0.960, 1.224)	0.229
$PM_{2.5}$ + SO_2			
$PM_{2.5}$	lag0	1.115 (1.010, 1.230)	0.086
	lag1	0.901 (0.804, 1.010)	0.131
	lag2	0.998 (0.893, 1.115)	0.964
	lag3	1.182 (1.058, 1.320)	0.035
	lag4	0.847 (0.755, 0.949)	0.059
	lag5	0.973 (0.872, 1.087)	0.580
	lag6	1.082 (0.973, 1.202)	0.192
	lag7	1.017 (0.939, 1.100)	0.629
SO_2	lag0	0.670 (0.393, 1.141)	0.188
	lag1	0.969 (0.581, 1.617)	0.872
	lag2	0.828 (0.501, 1.368)	0.434
	lag3	1.884 (1.159, 3.063)	0.045
	lag4	0.666 (0.401, 1.105)	0.168
	lag5	0.649 (0.393, 1.071)	0.147
	lag6	1.203 (0.745, 1.944)	0.425
	lag7	0.952 (0.622, 1.457)	0.774

RRs were estimates based on per 20 μg/m^3 increase in $PM_{2.5}$, PM_{10}, NO_2, and SO_2. [a]Distributed lag nonlinear models adjusted for average temperature and relative humidity

outcomes (Liu et al. 2019; Yang et al. 2020). The advantage value of case-crossover design is to control unobservable factors, i.e., the constant individual characteristics, such as maternal age at conception, living behaviors, season, and race (Ananth et al. 2018; Janes et al. 2005; Leiser et al. 2019). So the research results are reasonable and relatively reliable.

Additionally, some previous studies on air pollutants affecting adverse pregnancy outcomes, including spontaneous pregnancy loss, focused on exposure time in early pregnancy (Friedrich 2014; Hou et al. 2014; Patelarou and Kelly 2014). In this study, the short-term exposure windows before or at fertilization time were paid more attention, to attempt to assess the acute health effects of ambient air pollutants. Results indicated lag 3 day was the most statistically significant time for $PM_{2.5}$, PM_{10}, and SO_2. In particular, the sensitive exposure time window for NO_2 was lag 0 day both in crude and adjusted models.

The mechanism underlying the effect of air pollutants exposure on spontaneous abortion is still a matter of debate (Conforti et al. 2018; Jia and Guo 2014). Many studies reported the opinion that air pollutants had the effect of promoting oxidative stress and inflammatory processes (Grippo et al. 2018; Liang et al. 2020; Mahalingaiah 2018). Miscarriage may occur if there was an imbalance between active oxygen species and antioxidant defense system in embryonic tissues (Red et al. 2011). Some literature hypothesized that the result was caused by the mimic effect to androgens and estrogens of air pollutants in humans. The endocrine disruptors of air pollutants can act through classical nuclear receptors, but also through estrogen-related receptors, membrane-bound estrogen-receptors, and interaction with targets in the cytosol resulting in activation of the Src/Ras/Erk pathway and contributing to infertility (De Coster and van Larebeke 2012). In addition, some animal experimental studies have demonstrated that $PM_{2.5}$ and PM_{10} exposure can increase oxidative stress (Blum et al. 2017; Li et al. 2013). The academic opinion about the genotoxic effect and DNA methylation influenced by air pollutants is also discussed a lot (Perin et al. 2010b). Therefore, according to the previous studies, our findings are biologically plausible.

This study has some limitations. First, we estimated ambient air pollutants exposure at residential addresses instead of actual personal exposure which may result in measurement error or bias. However, we have estimated the personal exposure value accurately by using inverse distance weighting for each woman and each day. Second, the lack of individual-level data in the medical record including socioeconomic condition, maternal education, and information on personal risk factors such as cigarette smoking, drinking, and diseases histories may lead to a potential bias in the results. Fortunately, a larger sample

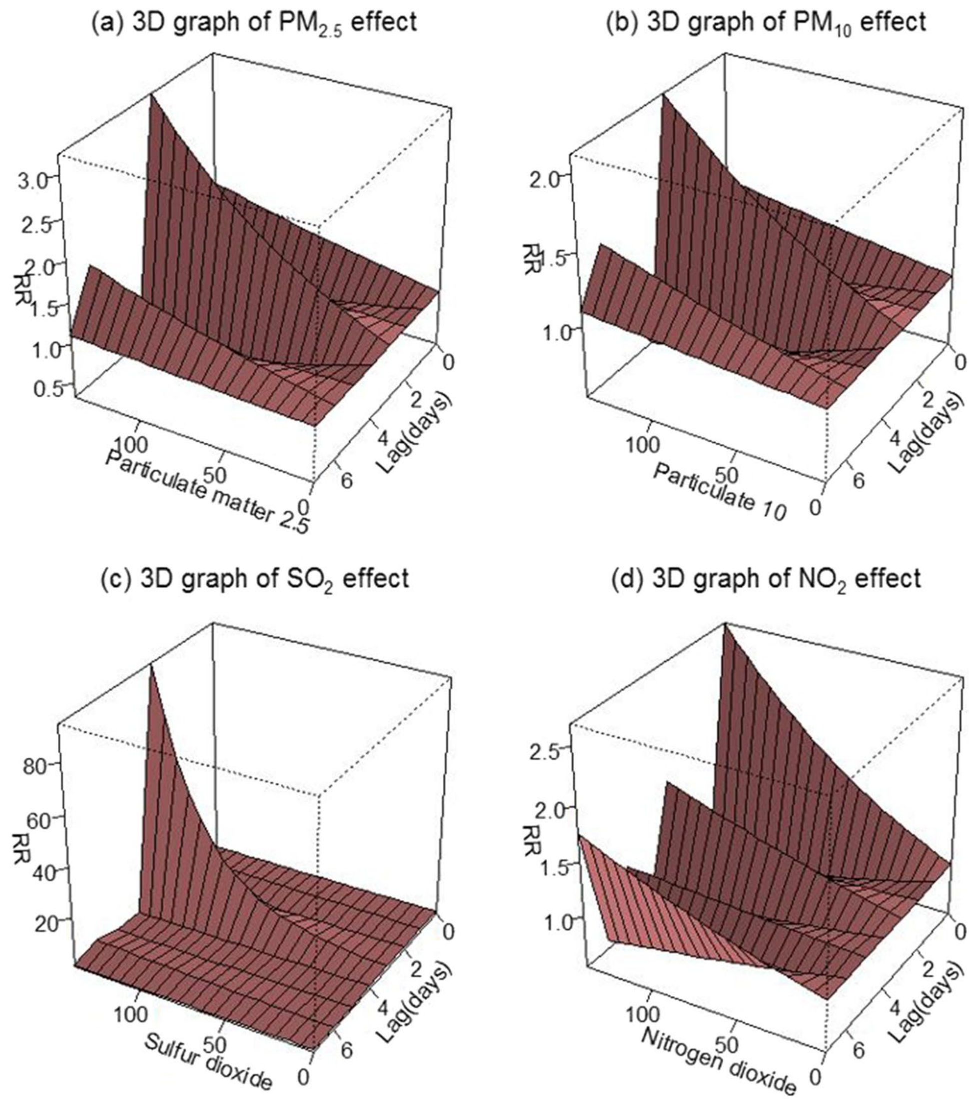

Fig. 2 Rate ratio of spontaneous abortions associated with a 20-unit increase in air pollutant levels for different single-day lags of lag 0–7 days

size was applied to adjust the bias to some extent. Third, this study only selected women cared in the CQHCWC. There were some women may have sought outpatient care in other hospitals. Additionally, some patients with early miscarriages may have been missed in medical records if the woman is unaware of the pregnancy (Moridi et al. 2014; Perin et al. 2010a). Furthermore, it only explored lag days 0–7 exposure time windows for estimating acute effect in this study. More sensitive exposure time windows during the whole pregnancy period should be further researched.

Conclusion

In summary, this study demonstrated that maternal exposure to high levels of $PM_{2.5}$, PM_{10}, NO_2, and SO_2 may increase the risk of spontaneous abortion through special air quality changes, a large sample size, and precise individual exposure assessment. It may have acute harmful effects and lag effects on pregnancy outcomes a few days before fertilization. Further research to explore sensitive exposure time windows is needed. Should we propose ideas and schemes to reduce the adverse effects of ambient air pollutants on pregnancy outcomes.

Author contribution WZ: Data curation, writing-original draft, and conceptualization. XM: Formal analysis, methodology, and software. QC: Visualization and writing-review and editing. PY: Writing-original draft and supervision. XL: Data curation, writing-review and editing, and conceptualization.

Funding This work was supported by the Association between Exposure to Ambient Air Pollution and Premature Birth and Low Birth Weight Outcomes in Chongqing Based on Birth Cohort [grant number: cstc2020jcyj-msxmX0511].

Data availability The datasets that support the findings of this study are openly available from the corresponding author on reasonable request.

Declarations

Ethics approval This study was approved by the institutional ethical committee board of CHCWC.

Consent for publication We do not have any individual person's data in any form.

Competing interests The authors declare no competing interests.

References

Ananth CV, Kioumourtzoglou MA, Huang Y, Ross Z, Friedman AM, Williams MA et al (2018) Exposures to air pollution and risk of acute-onset placental abruption: a case-crossover study. Epidemiology 29:631–638

Bekkar B, Pacheco S, Basu R, DeNicola N. 2020. Association of air pollution and heat exposure with preterm birth, low birth weight, and stillbirth in the us a systematic review. Jama Network Open 3.

Blum JL, Chen LC, Zelikoff JT (2017) Exposure to ambient particulate matter during specific gestational periods produces adverse obstetric consequences in mice. Environ Health Perspect 125:077020

Chen J, Fang J, Zhang Y, Xu Z, Byun HM, Li PH et al (2021) Associations of adverse pregnancy outcomes with high ambient air pollution exposure: results from the project elefant. Sci Total Environ 761:143218

Conforti A, Mascia M, Cioffi G, De Angelis C, Coppola G, De Rosa P et al (2018) Air pollution and female fertility: a systematic review of literature. Reprod Biol Endocrinol 16:117

Dastoorpoor M, Idani E, Goudarzi G, Khanjani N (2018) Acute effects of air pollution on spontaneous abortion, premature delivery, and stillbirth in ahvaz, iran: a time-series study. Environ Sci Pollut Res Int 25:5447–5458

De Coster S, van Larebeke N. 2012. Endocrine-disrupting chemicals: associated disorders and mechanisms of action. J Environ Public Health 2012:713696

DeVilbiss EA, Mumford SL, Sjaarda LA, Connell MT, Plowden TC, Andriessen VC, et al. 2020. Prediction of pregnancy loss by early first trimester ultrasound characteristics. Am J Obstet Gynecol 223.

Di Ciaula A, Bilancia M (2015a) Relationships between mild pm10 and ozone urban air levels and spontaneous abortion: clues for primary prevention. Int J Environ Health Res 25:640–655

Enkhmaa D, Warburton N, Javzandulam B, Uyanga J, Khishigsuren Y, Lodoysamba S et al (2014a) Seasonal ambient air pollution correlates strongly with spontaneous abortion in mongolia. BMC Pregnancy Childbirth 14:146

Enkhmaa D, Warburton N, Javzandulam B, Uyanga J, Khishigsuren Y, Lodoysamba S, et al. 2014b. Seasonal ambient air pollution correlates strongly with spontaneous abortion in mongolia. Bmc Pregnancy Childb 14.

Eroglu S, Colak E, Erinanc OH, Ozdemir D, Ceran MU, Tasdemir U, et al. 2020. Serum and placental periostin levels in women with early pregnancy loss. J Reprod Immunol 140.

Fang J, Kang CM, Osorio-Yanez C, Barrow TM, Zhang R, Zhang Y et al (2020) Prenatal pm2.5 exposure and the risk of adverse births outcomes: results from project elefant. Environ Res 191:110232

Friedrich MJ (2014) Spontaneous abortions in mongolia linked to high air pollutant levels. Jama-J Am Med Assoc 311:2372–2372

Frutos V, Gonzalez-Comadran M, Sola I, Jacquemin B, Carreras R, Checa Vizcaino MA (2015) Impact of air pollution on fertility: a systematic review. Gynecol Endocrinol 31:7–13

Gaskins AJ, Hart JE, Chavarro JE, Missmer SA, Rich-Edwards JW, Laden F et al (2019) Air pollution exposure and risk of spontaneous abortion in the nurses' health study ii. Hum Reprod 34:1809–1817

Grippo A, Zhang J, Chu L, Guo YJ, Qiao LH, Zhang J et al (2018) Air pollution exposure during pregnancy and spontaneous abortion and stillbirth. Rev Environ Health 33:247–264

Guo LQ, Chen Y, Mi BB, Dang SN, Zhao DD, Liu R et al (2019a) Ambient air pollution and adverse birth outcomes: a systematic review and meta-analysis. J Zhejiang Univ-Sc B 20:238–252

Guo P, Miao HZ, Chen YL, Fu Y, Wu YT, Zhao QG et al (2019b) Maternal exposure to gaseous ambient air pollutants increases the risk of preterm birth in the pearl river delta, china 2014–2017. Sci Total Environ 671:959–970

Ha S, Mendola P (2019) Opportunities and challenges for population-based studies investigating the effects of air pollution on pregnancy loss. Fertil Steril 111:256–257

Hou HY, Wang D, Zou XP, Yang ZH, Li TC, Chen YQ (2014) Does ambient air pollutants increase the risk of fetal loss? A case-control study. Arch Gynecol Obstet 289:285–291

Janes H, Sheppard L, Lumley T (2005) Case–crossover analyses of air pollution exposure data referent selection strategies and their implications for bias. Epidemiology 16:717–726

Jia X, Guo X (2014) Bibliometric analysis of associations between ambient pollution and reproductive and developmental health. Zhonghua Yu Fang Yi Xue Za Zhi 48:521–526

Leiser CL, Hanson HA, Sawyer K, Steenblik J, Al-Dulaimi R, Madsen T et al (2019) Acute effects of air pollutants on spontaneous pregnancy loss: a case-crossover study. Fertil Steril 111:341–347

Li CM, Li XZ, Suzuki AK, Zhang YH, Fujitani Y, Nagaoka K et al (2013) Effects of exposure to nanoparticle-rich diesel exhaust on pregnancy in rats. J Reprod Dev 59:145–150

Li XY, Huang SQ, Jiao AQ, Yang XH, Yun JF, Wang YX et al (2017) Association between ambient fine particulate matter and preterm birth or term low birth weight: an updated systematic review and meta-analysis. Environ Pollut 227:596–605

Liang F, Huo XN, Wang W, Li Y, Zhang J, Feng Y, et al. 2020. Association of bisphenol a or bisphenol s exposure with oxidative stress and immune disturbance among unexplained recurrent spontaneous abortion women. Chemosphere 257.

Liang Z, Yang Y, Qian Z, Ruan Z, Chang J, Vaughn MG et al (2019) Ambient pm2.5 and birth outcomes: estimating the association and attributable risk using a birth cohort study in nine chinese cities. Environ Int 126:329–335

Liu C, Li Q, Yan L, Wang H, Yu J, Tang J et al (2019) The association between maternal exposure to ambient particulate matter of 2.5mum or less during pregnancy and fetal congenital anomalies in yinchuan, china: a population-based cohort study. Environ Int 122:316–321

Mahalingaiah S (2018) Is there a common mechanism underlying air pollution exposures and reproductive outcomes noted in epidemiologic and in vitro fertilization lab-based studies? Fertil Steril 109:68

Moridi M, Ziaei S, Kazemnejad A (2014) Exposure to ambient air pollutants and spontaneous abortion. J Obstet Gynaecol Res 40:743–748

Patelarou E, Kelly FJ (2014) Indoor exposure and adverse birth outcomes related to fetal growth, miscarriage and prematurity-a systematic review. Int J Environ Res Public Health 11:5904–5933

Perin PM, Maluf M, Czeresnia CE, Januario DA, Saldiva PH (2010a) Impact of short-term preconceptional exposure to particulate air pollution on treatment outcome in couples undergoing in vitro fertilization and embryo transfer (ivf/et). J Assist Reprod Genet 27:371–382

Perin PM, Maluf M, Czeresnia CE, Nicolosi Foltran Januario DA, Nascimento Saldiva PH (2010b) Effects of exposure to high levels of particulate air pollution during the follicular phase of the conception cycle on pregnancy outcome in couples undergoing in vitro fertilization and embryo transfer. Fertil Steril 93:301–303

Raz R, Kioumourtzoglou MA, Weisskopf MG (2018) Live-birth bias and observed associations between air pollution and autism. Am J Epidemiol 187:2292–2296

Red RT, Richards SM, Torres C, Adair CD (2011) Environmental toxicant exposure during pregnancy. Obstet Gynecol Surv 66:159–169

Sileo FG, Kulkarni A, Branescu I, Homfray T, Dempsey E, Mansour S, et al. Non-immune fetal hydrops: etiology and outcome according to gestational age at diagnosis. Ultrasound in Obstetrics & Gynecology.

Wdowiak A, Wdowiak E, Bojar I, Bakalczuk G (2018) The influence of air pollution on human reproduction. Postepy Higieny I Medycyny Doswiadczalnej 72:35–42

Xue T, Zhang Q (2018) Associating ambient exposure to fine particles and human fertility rates in china. Environ Pollut 235:497–504

Yang Y, Lin Q, Liang Y, Ruan Z, Acharya BK, Zhang S, et al. 2020. Maternal air pollution exposure associated with risk of congenital heart defect in pre-pregnancy overweighted women. Sci Total Enviro 712.

Zhang KL, Lu YF, Zhao HP, Guo J, Gehendra M, Qiu HY et al (2016) Association between atmospheric particulate matter and adverse pregnancy outcomes in the population. Int J Clin Exp Med 9:20594–20604

Zhang Y, Wang J, Chen L, Yang H, Zhang B, Wang Q et al (2019) Ambient pm2.5 and clinically recognized early pregnancy loss: a case-control study with spatiotemporal exposure predictions. Environ Int 126:422–429

Zhu XX, Liu Y, Chen YY, Yao CJ, Che Z, Cao JY (2015) Maternal exposure to fine particulate matter (pm2.5) and pregnancy outcomes: a meta-analysis. Environ Sci Pollut R 22:3383–3396

Authors and Affiliations

Wenzheng Zhou[1] · Xin Ming[1] · Qing Chen[2] · Xiaoli Liu[1] · Ping Yin[3]

[1] Chongqing Health Center for Women and Children, Chongqing 401147, China

[2] Institute of Toxicology, College of Preventive Medicine, Army Medical University (Third Military Medical University), Chongqing 400038, China

[3] School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China