Environmental Research 176 (2019) 108531

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Associations between ambient air pollution and mortality from all causes, pneumonia, and congenital heart diseases among children aged under 5 years in Beijing, China: A population-based time series study

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ARTICLE INFO

Keywords:
Ambient air pollution
Time series study
Children aged < 5 years
Generalized additive Poisson regression

ABSTRACT

Background: Previous studies have mainly focused on the associations between particulate matters and infant mortality. However, evidence regarding the associations between gaseous pollutants and mortality among children aged < 5 years remains sparse.

Objectives: The aim of this study was to investigate the associations between ambient air pollution and death among children aged < 5 years in Beijing, China, and explore the impact of age, gender and specific causes of death on these associations.

Methods: Concentrations of ambient air pollution and the number of deaths among children aged < 5 years in Beijing from January 2014 to September 2016 were extracted from authoritative electronic databases. The associations were estimated for a single-month lag from the current month up to the previous 5 months (lag0-lag5) and moving averages of the current and previous months (lag01-lag05) using generalized additive Poisson regression (adjusted for time trends, season, meteorological variables and holidays). Subgroup analyses related to age, gender and specific diseases were performed. Two-pollutant models were used to evaluate the possible role of single pollutants.

Results: Sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and carbon monoxide (CO) demonstrated the strongest associations with death among children aged < 5 years at lag0, and the estimates decreased or even turned negative with the increasing lag periods. For an interquartile range increase in SO_2, NO_2 and CO at lag0, the odds ratios (OR) were 1.332 (95% CI 1.152-1.539), 1.383 (95% CI 1.113-1.718) and 1.273 (95% CI 1.028-1.575). However, CO lost significance after adjusting for SO_2 and NO_2, and $PM_{2.5}$ gained significance (OR 1.548, 95% CI 1.061-2.258) after adjusting for PM_{10}. The ORs for SO_2 and NO_2 remained the most stable across all two-pollutant models. The associations for children aged 1–5 years were stronger than those reported for infants at lag0 but lower at the other lag months. The pollutant associations were stronger for congenital heart disease-related death than overall and pneumonia-related death. We did not find significant differences in terms of gender.

Conclusion: Exposure to air pollution may increase the incidence of death among children aged < 5 years. SO_2 and NO_2 may be the most stable pollutants reflecting associations between air pollution and death, deserving further attention. Children with congenital heart diseases are more susceptible to air pollution. Therefore, it is urgent to implement the clean air targets established by WHO and reduce the exposure of children to air pollution.

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https://doi.org/10.1016/j.envres.2019.108531
Received 22 January 2019; Received in revised form 6 June 2019; Accepted 8 June 2019
Available online 11 June 2019
0013-9351/

1. Introduction

Air pollution has become a common global problem that can no longer be ignored. Owing to the rapid socioeconomic development, the levels of ambient air pollution have increased in developing Asian countries, especially in several Chinese megacities (Zhang et al., 2016). In Beijing, the capital of China, the mean annual concentrations of $PM_{2.5}$ (particulate matter < 2.5 μm in aerodynamic diameter), PM_{10} (particulate matter < 10 μm in aerodynamic diameter), and nitrogen dioxide (NO_2) exceed the values indicated by the World Health Organization (WHO) Air Quality Guidelines (AQG) (WHO, 2005). Therefore, studying the associations between ambient air pollution and health in Beijing is of great importance.

Numerous studies have found that ambient air pollutants were associated with various adverse health effects, ranging from subclinical outcomes to death (Dominici et al., 2006; Li et al. 2017a, 2017b; Molter et al., 2015; Wu et al., 2016). Children are more susceptible to air pollution than adults due to their immature lungs and immune systems (Kim, 2004; Landrigan et al., 2018; Lelieveld et al., 2018). Therefore, the associations between air pollution and health of children are of particular interest and concern.

Infant mortality and mortality among children aged < 5 years are two important indicators, which represent health situation of children in a particular area (Chengye, 2012). A case-crossover study found that a 10 $\mu g/m^3$ increase in daily $PM_{2.5}$ concentrations was associated with odds ratios (OR) of 1.06 (95% confidence interval [CI] 1.01–1.12) for infant mortality and 1.10 (95%CI 1.02–1.19) for post-neonatal mortality (Yorifuji et al., 2016). A pregnancy and lifetime exposure study also found that total infant, respiratory and sudden infant death syndrome (SIDS) mortality were significantly associated with exposure to $PM_{2.5}$ (Son et al., 2017). Most previous studies adopted particulate matters ($PM_{2.5}$ and PM_{10}) as indicators of exposure (Gouveia and Junger, 2018; Heft-Neal et al., 2018; Son et al., 2017; Yorifuji et al., 2016). Although studies have evaluated the associations of gaseous contaminants, such as sulfur dioxide (SO_2), NO_2 and carbon monoxide (CO), the results were inconsistent (Hajat et al., 2007; Ritz et al., 2006). Moreover, studies conducted thus far focused on the associations between pollution and infant mortality. To our knowledge, only two studies have investigated the associations for the total mortality among children aged < 5 years, an indicator as important as infant mortality (Lelieveld et al., 2018; Owili et al., 2017). Therefore, further investigations regarding the associations between gaseous pollutants and mortality among children aged < 5 years are warranted.

The Beijing Under-5 Mortality Rate Surveillance Network covers all children aged < 5 years in Beijing, providing data on overall death among children in this age group. Additionally, the Beijing Environmental Monitoring Center provides data on the concentrations of both continuous ambient particulate matters ($PM_{2.5}$ and PM_{10}) and gaseous pollutants (SO_2, NO_2, CO, and ozone [O_3]). The aim of this study was to investigate the associations between the concentrations of ambient $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 and overall death among children aged < 5 years in Beijing, China. Subgroup analyses related to age, gender, and specific diseases were also conducted.

2. Methods

2.1. Data collection

2.1.1. Death data

We obtained overall death data for children aged < 5 years from January 2014 to September 2016. These were surveillance data from the electronic Death Recording Cards of the Beijing Under-5 Mortality Rate Surveillance Network (http://www.mchscn.org/). This monitoring system covers all children aged < 5 years in all 16 districts of Beijing (i.e., Dongcheng, Xicheng, Haidian, Chaoyang, Fengtai, Shijingshan, Mentougou, Fangshan, Daxing, Shunyi, Huairou, Miyun, Yanqing, Changping, Pinggu, and Tongzhou). Stringent quality control methods were applied to the surveillance system using a three-level network approach (i.e., community/hospital, district, and municipal level). The under-reporting rate of death in Beijing was < 0.5% over the last 10 years. More specific information regarding the surveillance system was provided in our previous study (Cao et al., 2017).

Regarding the death data, the extracted information for each child included age, gender, date of birth, date of death, and classification of the causes of death. Categorization of the causes of death was in accordance with the International Classification of Diseases 10th Revision (ICD-10). Subsequently, we counted the number of deaths according to the date of death, and eliminated accidental death (i.e., without relation to ambient air pollution). Accidental death included drowning, traffic accident, accidental asphyxia, poisoning and fall. Furthermore, we divided overall deaths among children aged < 5 years into subgroups based on age, gender, and cause of death.

Because the death data (surveillance data) were derived from the Beijing Under-5 Mortality Surveillance Network, there was no requirement for informed consent. This study was approved by the Ethical Committee of Capital Medical University (Beijing, China), and was performed in compliance with the tenets of the Declaration of Helsinki.

2.1.2. Ambient air pollution data

To ensure sufficient spatial variation in the measured concentrations, routine monitoring data on ambient air pollutants were obtained from 35 air quality monitoring stations, that belong to the Beijing Environmental Monitoring Center (http://zx.bjmemc.com.cn/) and collect data in real time. These stations are distributed across the 16 districts of Beijing and divided into four categories: 12 urban environmental evaluation sites, 16 suburban environmental evaluation sites, 5 traffic pollution monitoring sites, and 2 regional background control sites. The distribution of the sites is described in Fig. 1.

Continuous hourly concentrations were gathered from January 2014 to September 2016. The mean levels of $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 were averaged for each monitoring station and day. The daily mean levels of these pollutants at each station were used only if > 20 of the 24-hourly measurements were available, in accordance with the China Ambient Air Quality Standards (GB 3095-2012). For missing data, we used linear interpolation for each station to better predict the daily mean concentrations. Linear interpolation is a common method used for imputing missing time series data, with acceptable performance and reliability (Zhang, 2016). The monthly concentration of air pollutants in each child was subsequently calculated according to the date of death. The total exposure of one month was the mean of the concentrations in each child who expired in the same month. Concentrations of all pollutants were expressed in $\mu g/m^3$, except for CO, which was expressed in mg/m^3.

2.1.3. Meteorological data

Data on the daily mean ambient temperature and relative humidity during the study period (without missing data) were obtained from the National Meteorological Information Center (http://data.cma.cn/). Monthly means were calculated.

2.2. Statistical analysis

The correlations between the concentrations of ambient air pollutants and meteorological variables during the study period were analyzed using Spearman's correlation coefficient. This approach was used due to the non-normal distribution of the data.

The monthly number of deaths among children aged < 5 years was low, and approximately followed a Poisson distribution. Therefore, the associations between ambient air pollution and death were investigated using generalized additive Poisson regression with a log-link function and adjusted for potential confounders. Penalized cubic regression

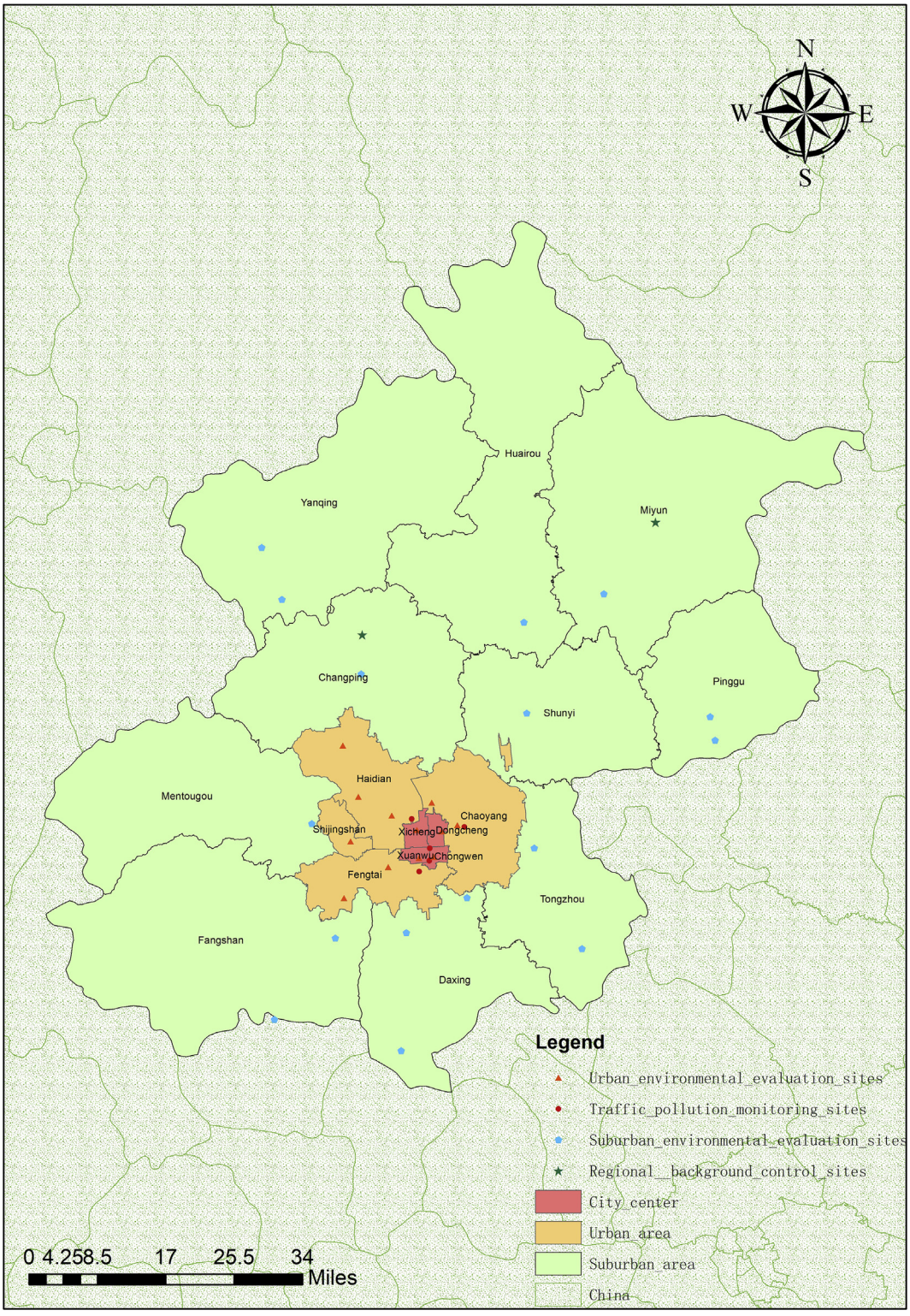


Fig. 1. Spatial distribution of the air quality monitoring stations in Beijing, China.

splines were used to capture time trends. We used the partial auto-correction function (PACF) of the residuals to determine the number of degrees of freedom for the spline function of time. Finally, we selected seven degrees of freedom per year in the spline function of time for all pollutants. We included the following potential confounders in the models: monthly mean temperature, relative humidity, and categorical variables for year, season, and public holiday months (i.e., months with > 7 days of government holidays, excluding weekends). We adjusted for meteorological factors averaged over the same month and the previous month, and over the 6 months preceding this period. The best averaging period for meteorological factors was selected according to the generalized cross-validation (GCV) values which measure models fit. In all models, three degrees of freedom were used for the spline function of temperature and relative humidity, which reportedly allowed adequate control for their effects on health outcomes (Samet et al., 2000). Year and season were treated as categorical variables with

values of 0 (2014), 1 (2015), and 2 (2016), and 0 (warm season, May–October) and 1 (cold season, November–April), respectively. Regarding the concentrations of air pollutants, we estimated the associations with different lag structures using a single-month lag from the current month up to the previous 5 months (lag0–lag5), as well as moving averages of the current and previous months (lag01–lag05). To facilitate comparisons across pollutants, the associations between air pollutants and overall death among children aged < 5 years were reported as OR with 95%CI for an interquartile range (IQR) increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3 concentrations.

Furthermore, we performed subgroup analyses, and estimated the age-specific associations between air pollutants and death. Analyses were performed for infants (< 1 year) and children aged 1–5 years. The analyses were also stratified by gender to evaluate potential effect modifications and determine susceptible populations. Regarding the causes of death, we conducted subgroup analyses to explore disease-specific associations. Pneumonia (ICD-10: J12–J18) and congenital heart diseases (CHD) (ICD-10: Q24) were investigated because they were the leading causes of death among children aged < 5 years during the study period (2014–2016) (Cao et al., 2017), and previous studies also showed that the associations of ambient air pollutants mainly and directly targeted the cardiorespiratory system (Li et al., 2018; Liu et al., 2017; Nhung et al., 2017; Yang et al., 2017).

In addition, we used two-pollutant models for all pollutants (i.e., $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO and O_3) without interactions to determine the possible role of single pollutants. To evaluate the multicollinearity in the models, we calculated the variance inflation factor (VIF). The results for all pairs of pollutants were clearly below the threshold of 10, which indicated the lack of strong multicollinearity (Supplementary Table A1).

In the sensitivity analyses, we a) excluded children who were alive for < 1 month; b) used four degrees of freedom in meteorological factors; and c) varied the level of smoothness of the time trend function (with six to eight degrees of freedom per year) to explore the stability of the associations between air pollutants and deaths among children aged < 5 years.

All statistical analyses were conducted using the SAS version 9.4 (https://www.sas.com) and the visualization of the results were conducted using the GraphPad Prism version 8 (https://www.graphpad.com). Statistical significance was defined as a two-tailed p-value < 0.05.

3. Results

3.1. Descriptive statistics for overall death, pollutants and meteorological variables

Descriptive statistics for monthly number of deaths, air pollutant concentrations, and meteorological variables are presented in Table 1. We examined 1236 deaths (about 37.5 deaths per month) among children aged < 5 years from January 2014 to September 2016. Death among infants (< 1 year) accounted for 85.3%, and the monthly mean was 31.9. Death among males accounted for 54.1% and the monthly mean was 20.3. Death due to pneumonia and congenital heart diseases (CHD) accounted for 6.0% and 12.5%, respectively. The monthly mean number of deaths associated with these two diseases were 2.2 and 4.7. Monthly number of deaths were all higher in the cold season.

The monthly mean concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3 and CO were 80.7, 111.0, 16.7, 49.7, and 64.7 μg/m^3, and 1.3 mg/m^3, respectively. Fig. 2 illustrates the time trends for all air pollutants. Most concentrations of air pollutants showed clear seasonal trends (i.e., higher in the cold season and lower in the warm season). However, the concentrations of O_3, showed an inverse trend. As shown in Table 2, the monthly concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO were strongly and positively correlated with each other. In contrast, the concentration of O_3 was moderately and negatively correlated with those of the other pollutants. Moreover, temperature and relative humidity were negatively correlated with all air pollutants except for O_3 ($r_{tem\text{-}O3}$ = 0.85; $r_{hum\text{-}O3}$ = 0.24).

3.2. Associations between air pollutants and overall death

Fig. 3 shows the OR of overall death among children aged < 5 years per an IQR increase in the concentrations of air pollutants with different lag structures. For the current-month average (lag0), the number of overall deaths was positively associated with all pollutants. However, statistically significant associations were observed only for SO_2 (OR 1.332, 95% CI 1.152-1.539), NO_2 (OR 1.383, 95% CI 1.113-1.718), and CO (OR 1.273, 95% CI 1.028-1.575). For the moving averages, positive significant associations were observed for SO_2 at lag01, CO at lag02, $PM_{2.5}$ and NO_2 at both lag01 and lag02, and PM_{10} at lag01-lag03. All pollutants showed the strongest estimates at lag0 among the single-month exposures, and the strongest estimates were observed for $PM_{2.5}$, SO_2 and NO_2 at lag01 among the moving average exposures. At lag0 and lag01, the strongest associations were observed for NO_2 among overall air pollutants.

3.3. Subgroup analyses by age, gender, and diseases

Fig. 4 illustrates age-specific OR for overall death among children aged 0–5 years, infants (< 1 year), and those aged 1–5 years. For the current month (lag0), the number of deaths was positively associated with all pollutants in all age groups, except for O_3 among children aged 1–5 years. All pollutant estimates of children aged 1–5 years were higher than those for infants, except for O_3. In contrast, for the previous months (lag1 and lag2) as well as the 2- and 3-month moving averages (lag01 and lag02), all pollutant estimates for infants were higher than those reported for children aged 1–5 years, except for $PM_{2.5}$ at lag2 and O_3 at lag1. In particular, for infants, significant positive associations were observed for $PM_{2.5}$, SO_2, NO_2 and CO at lag1. In contrast, negative associations were observed for children aged 1–5 years at the same lag structure (lag1), except for O_3.

Gender-specific OR for overall death among male and female children are also summarized in Fig. 4. The associations of pollutants were higher for females than males, except for SO_2 and O_3, which was higher for males. However, there were no statistically significant differences between males and females (p > 0.05).

Table 3 summarizes disease-specific OR for death due to pneumonia and congenital heart diseases (CHD) among children aged < 5 years. Regarding pneumonia, significant positive associations were observed for NO_2 at lag0 (OR 1.740, 95% CI 1.057-2.865). O_3 exhibited significant negative associations with pneumonia-related death at both lag0 and lag01 (lag0: OR 0.418, 95% CI 0.237-0.738; lag01: OR 0.455, 95% CI 0.398-0.519). Regarding CHD, $PM_{2.5}$ (OR 1.653, 95% CI 1.083-2.523), PM_{10} (OR 1.741, 95% CI 1.085-2.796) and CO (OR 1.604, 95% CI 1.058-2.433) at lag0, and SO_2 (lag0: OR 2.362, 95% CI 1.594-3.500; lag01: OR 2.479, 95% CI 1.552-3.960) and NO_2 (lag0: OR 2.103, 95% CI 1.175-3.763; lag01: OR 2.239, 95% CI 1.043-4.806) at both lag0 and lag01 showed significant positive associations. All pollutants demonstrated stronger estimates on CHD-related death than overall and pneumonia-related death.

3.4. Sensitivity analyses

Two-pollutant models for overall, pneumonia-related and CHD-related death are presented in Fig. 5 and Supplementary Figure A1. The estimates for SO_2 and NO_2 were the most stable across all two-pollutant models of overall, pneumonia-related, and CHD-related death. In contrast, the estimates of $PM_{2.5}$, PM_{10}, and CO decreased after the inclusion of SO_2 or NO_2, especially the estimates of $PM_{2.5}$ and PM_{10} for CHD-related death, and those of CO for both overall and CHD-related death, which lost significance. Additionally, all associations between $PM_{2.5}$

Table 1
Descriptive statistics of the concentrations of air pollutants, meteorological variables, and death among children aged < 5 years from January 2014 to September 2016 in Beijing, China.

Variable	Total (%)	Mean	SD	Min	P25	Median	P75	Max	IQR	Season mean	
										Warm	Cold
										May–October	November–April
Monthly number of deaths											
Total	1236 (100.0)	37.5	12.6	13.0	28.0	36.0	46.0	67.0	18.0	35.9	39.1
Infants (< 1 year)	1054 (85.3)	31.9	11.1	9.0	22.0	31.0	40.0	56.0	18.0	31.2	32.7
1–5 years	182 (14.7)	5.5	2.9	1.0	3.0	6.0	7.0	13.0	4.0	4.7	6.4
Males	669 (54.1)	20.3	7.2	7.0	16.0	20.0	25.0	34.0	9.0	19.9	20.7
Females	567 (45.9)	17.2	6.1	6.0	15.0	16.0	20.0	33.0	5.0	16.1	18.4
Pneumonia (ICD 10: J12-J18)	74 (6.0)	2.2	2.0	0.0	1.0	2.0	3.0	10.0	2.0	1.5	3.0
Congenital heart diseases (ICD10: Q24)	154 (12.5)	4.7	2.8	0.0	3.0	4.0	7.0	11.0	4.0	4.4	4.9
Monthly air pollutant concentrations											
$PM_{2.5}$ ($\mu g/m^3$)	–	80.7	25.7	37.0	61.5	74.8	97.1	142.4	35.6	63.4	99.2
PM_{10} ($\mu g/m^3$)	–	111.0	27.8	56.7	91.1	109.8	134.0	161.6	42.9	93.0	130.2
SO_2 ($\mu g/m^3$)	–	16.7	13.4	3.6	7.4	12.9	21.9	50.6	14.5	7.7	26.3
NO_2 ($\mu g/m^3$)	–	49.7	10.6	33.6	41.2	48.1	58.1	68.1	16.9	42.2	57.7
CO (mg/m^3)	–	1.3	0.6	0.7	0.8	1.0	1.5	2.7	0.7	0.8	1.8
O_3 ($\mu g/m^3$)	–	64.7	30.0	17.6	39.3	63.5	94.0	125.3	54.7	83.3	45.0
Meteorological variables											
Monthly temperature (°C)	–	14.6	10.7	−4.2	3.6	16.9	24.9	28.1	21.3	23.3	5.3
Monthly humidity (%)	–	51.8	12.8	31.4	41.6	53.5	63.6	77.2	22.0	58.7	44.6

*$PM_{2.5}$, particulate matter < 2.5 μm in aerodynamic diameter; PM_{10}, particulate matter < 10 μm in aerodynamic diameter; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; SD, standardized deviation; Min, minimum; Max, maximum; P25, 25th percentile; P75, 75th percentile; IQR, interquartile range.

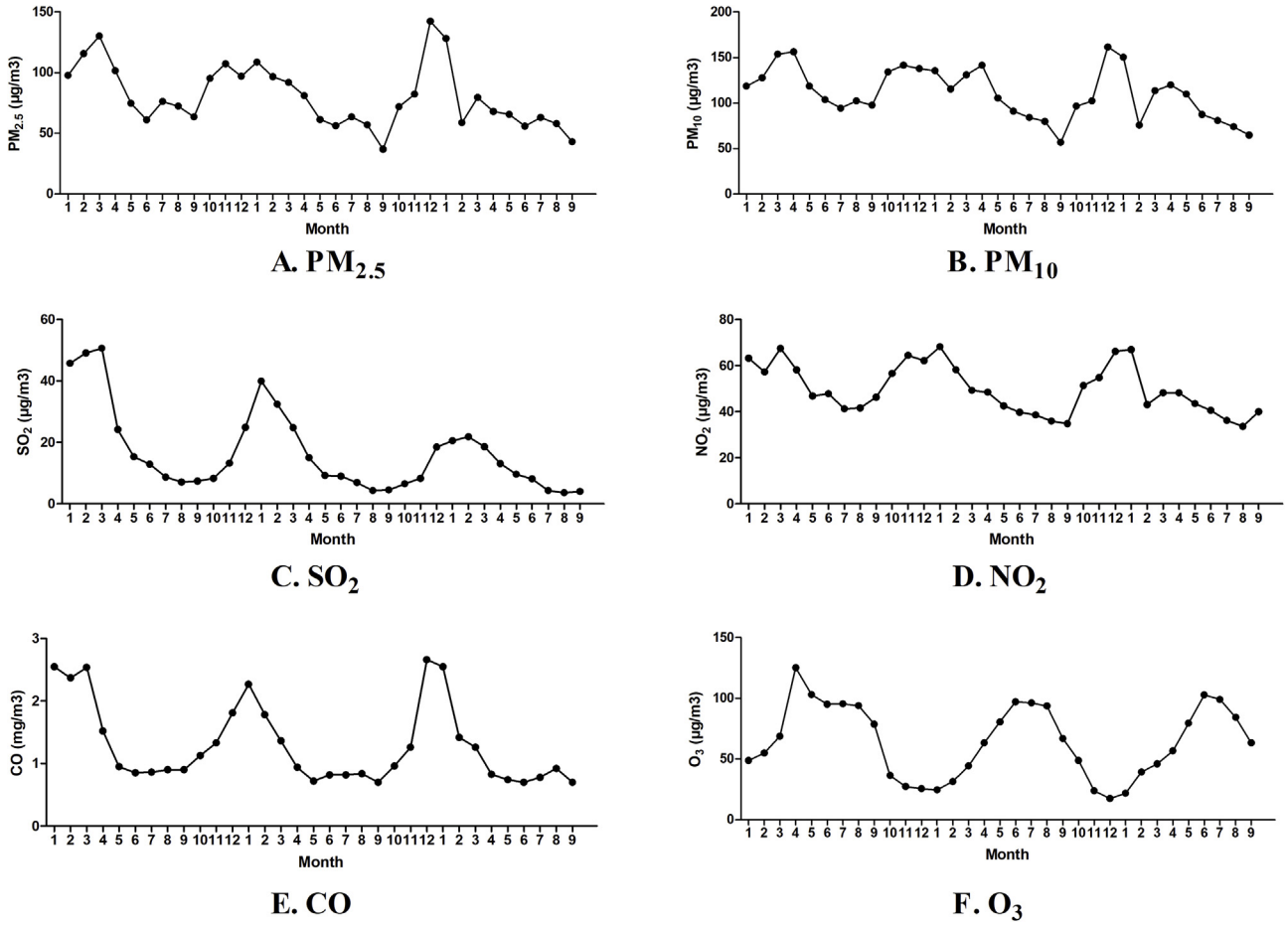
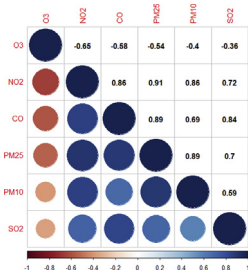


Fig. 2. Time series plots of the monthly mean concentrations of air pollutants from January 2014 to September 2016 in Beijing, China.

Table 2
Spearman's correlation coefficient between the monthly mean concentrations of air pollutants and meteorological variables.

Variable	O_3	NO_2	CO	$PM_{2.5}$	PM_{10}	SO_2	Tem[c]	Hum[d]
O_3	1.00	−0.65[a]	−0.58[a]	−0.54[a]	−0.40[b]	−0.36[b]	0.85[a]	0.24
NO_2	–	1.00	0.86[a]	0.91[a]	0.86[a]	0.72[a]	−0.85[a]	−0.46[b]
CO	–	–	1.00	0.89[a]	0.69[a]	0.84[a]	−0.81[a]	−0.40[b]
$PM_{2.5}$	–	-	–	1.00	0.89[a]	0.70[a]	−0.73[a]	−0.35[b]
PM_{10}	–	–	–	–	1.00	0.59[a]	−0.65[a]	−0.48[b]
SO_2	–	–	-	–	–	1.00	−0.76[a]	−0.74[a]
Tem[c]	–	–	–	–	–	–	1.00	0.48[b]
Hum[d]	–	–	–	–	–	–	–	1.00

Correlation between pollutants



[a] $p < 0.001$.
[b] $p < 0.05$.
[c] Tem: temperature.
[d] Hu: humidity.

and overall, pneumonia-related and CHD-related death increased after the inclusion of PM_{10}. For overall death, the estimates of $PM_{2.5}$ at lag0 acquired statistical significance (OR 1.548, 95% CI 1.061-2.258) after adjusting for PM_{10}. The significant negative associations between O_3 and pneumonia-related death remained after adjusting for the other pollutants.

Supplementary Figure A2 shows the results of the sensitivity analyses by excluding children who were alive for < 1 month. Significant associations remained stable for SO_2, NO_2 and CO. However, estimates for all pollutants (except O_3) decreased slightly after excluding children aged < 1 month at lag0. The estimates for $PM_{2.5}$ and PM_{10} lost statistical significance at lag01 and lag02. Other sensitivity analyses involved the use of four degrees of freedom in meteorological factors and variations in the level of smoothness of the time trend function (with six to eight degrees of freedom per year) (Supplementary Figure A3). All results were stable.

4. Discussion

In our study, the levels of ambient air pollution were relatively high in Beijing, China between January 2014 and September 2016. The monthly mean concentrations of $PM_{2.5}$ (80.7 μg/m^3), PM_{10} (111.0 μg/m^3) and NO_2 (49.7 μg/m^3) exceeded the WHO Air Quality Guidelines (AQG) values (i.e., 10 μg/m^3, 20 μg/m^3 and 40 μg/m^3). However, the concentrations of SO_2 and O_3 were within the AQG values.

Previous studies have found that ambient air pollutants were associated with adverse health effects (Dominici et al., 2006; Li et al. 2017a, 2017b; Molter et al., 2015; Wu et al., 2016). Biologically plausible mechanisms linking exposure to air pollution to adverse health outcomes include oxidative stress, systematic inflammation, blood coagulation, endothelial function, and hemodynamic responses (Fiordelisi et al., 2017; Kannan et al., 2006). Compared with adults, children exhibit different physiologic characteristics (i.e., immature lungs and immune systems), which may be associated with higher health risks (Glinianaia et al., 2004; Son et al., 2017). Therefore, children have been identified as susceptible populations to air pollution (Backes et al., 2013; Lelieveld et al., 2018).

A population-based time series analysis was used to assess the associations between ambient air pollution and death among children aged < 5 years in Beijing, China. The number of overall deaths was significantly associated with the levels of SO_2, NO_2 and CO. In addition, the strongest association estimates were observed for NO_2 among overall air pollutants at both lag0 and lag01. The results are consistent with those of previous studies indicating that the health of children is influenced by markers of primary traffic air pollutants, such as NO_2 and CO (Liu et al., 2017; Nhung et al., 2018; Tuan et al., 2015). A study performed by Litchfield et al. found that NO_2 exhibited stronger associations with infant death syndrome (SIDS) than other pollutants, of which an IQR (19.5 μg/m^3) increase in the daily concentrations of NO_2 was associated with a OR of 1.16 (95% CI 1.02-1.31) in SIDS (Litchfield et al., 2018). A study conducted by Ritz et al. also found that exposures to NO_2 and CO were significantly associated with increased post-neonatal death (Ritz et al., 2006). And Hajat et al. observed that infant death was strongly associated with daily exposure to SO_2 (Hajat et al., 2007). In our study, we observed a significant association with particulate matters ($PM_{2.5}$ and PM_{10}) among children aged < 5 years. Son et al. and Yorifuji et al. also found that life-time or daily exposures to $PM_{2.5}$ were associated with total infant and SIDS mortality (Son et al., 2017; Yorifuji et al., 2016). The majority of previous studies were performed in countries with low concentrations of pollutants. However, the levels of ambient air pollution in Beijing, China are relatively high. Moreover, in the present study, we used the number of overall deaths among children aged < 5 years as an outcome instead of infant death or SIDS. Therefore, the associations were stronger than those observed in previous studies. Notably, the OR were 1.332 (95% CI 1.152-1.539), 1.383 (95% CI 1.113-1.718) and 1.273 (95% CI 1.028-1.575) per an IQR increase in the concentrations of SO_2, NO_2 and CO, respectively.

Identifying the associations of ambient air pollution in different exposure windows is of great importance in the estimation of health risk. In our study, the associations of pollutants were diverse for different lag structures. Consistent with previous studies (Lin et al., 2013; Liu et al., 2017; Yorifuji et al., 2016), we found that exposure to air pollutants at the current-month (lag0) yielded the strongest estimates on death among children aged < 5 years. Moreover, these estimates decreased or even turned negative with the increasing lag periods, especially in SO_2, NO_2 and CO. This result indicates that children aged < 5 years are susceptible to the current exposures. The negative estimates at lag3-lag5 may be attributed to the harvesting at the current or shorter lags, that the increases in death all triggered by air pollution at the current (lag0) or shorter lags (lag1-lag2) instead of longer lags (lag3-lag5). Another time series study performed by Liu et al. also found the similar phenomenon that the associations between $PM_{2.5}$ and pediatric respiratory outpatient visits were positive at current-day and turned negative at 3 and 4 days lag (Liu et al., 2017). However, the mechanisms still require further research.

In our previous study, we found that the distribution of causes of death varied among children of different ages (Cao et al., 2017). Therefore, we also considered the age-specific associations in different exposure windows on the health of children. In the present study, we found that all significant associations for children aged 1–5 years were higher than those for infants at lag0 (the current month exposure). A previous study performed by Darrow et al. showed a similar pattern

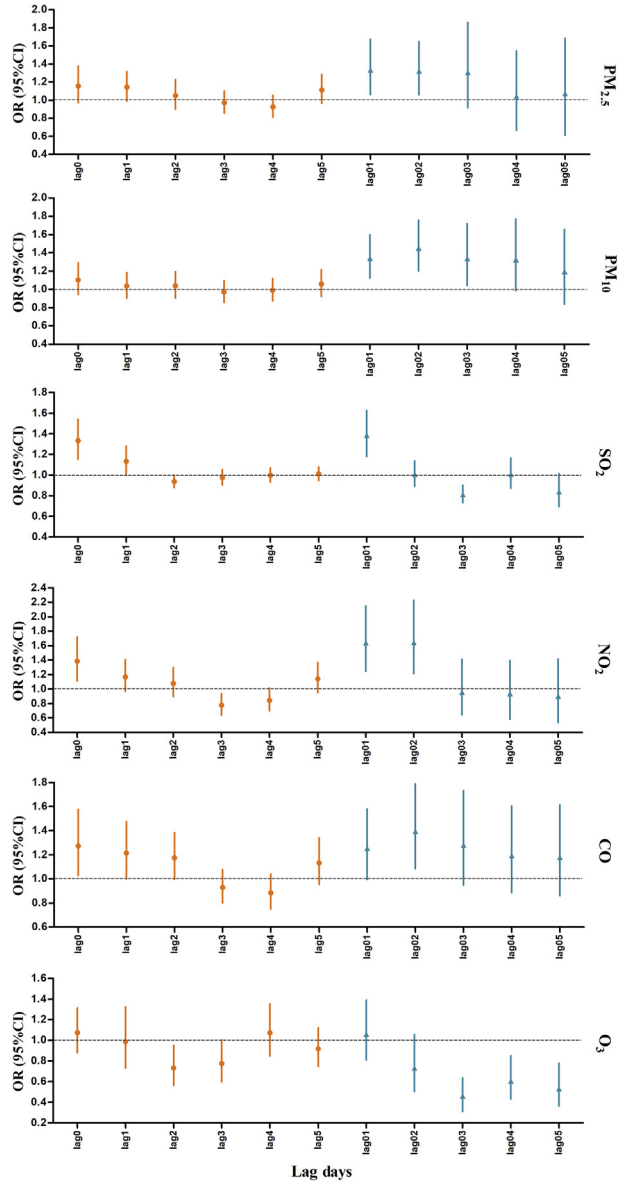


Fig. 3. Odds ratios with 95% confidence intervals per an interquartile range increase in the concentrations of air pollutants using different lag structures for overall death among children aged < 5 years in Beijing, China. *Orange circles: a single-month lag from the current month up to the previous 5 months (lag0-lag5). *Blue triangles: moving averages of the current and previous months (lag01-lag05).

(Darrow et al., 2014). In Beijing, infants (< 1 year) are usually kept indoors until they reach 1 year of age. In contrast, older children have increased exposure time due to outside exercise; thus, they may be more susceptible to the current effects of air pollution. In addition, for infants who were alive for < 1 month, the calculation of the levels of exposure to air pollution involved the prenatal period and may partly represent the exposure of the mothers. Therefore, the actual exposure levels of infants may be lower than the estimation, which resulted in the associations on children aged 1–5 years being more pronounced than those reported in infants. However, we did not observe this finding at other lag months.

We found that the associations between pollutants and infant deaths were more pronounced than those on children aged 1–5 years at lag1-lag2 (previous-month exposures) and lag01-lag02 (moving average exposures). Moreover, for infants, significant positive associations were observed for $PM_{2.5}$, SO_2, NO_2 and CO at lag1. In contrast, for children aged 1–5 years, negative associations were observed for both the previous-month exposures and moving average exposures. This result indicated that ambient air pollutants may exert lag and cumulative associations on infants, and the lag associations were covered by children aged 1–5 years when analyzed total under 5 years old children. Infants have more immature immune systems and little immunological memory (Basha et al., 2014; Kollmann et al., 2017), resulting in slower inflammatory responses and autoimmune injuries versus those of older children. Moreover, the respiratory rate of infants (> 30 breaths/min) is higher than those of other age groups (approximately 20–25 breaths/min) (Fleming et al., 2011). Furthermore, infants exhibit different patterns of breathing (i.e., mouth breathing), leading to higher inhaling doses of air pollutants versus older children after a longer duration. These characteristics may further amplify the susceptibility of infants to the lag and cumulative associations of air pollution. Because of the limited sample size in our study, the results may not be generalizable. Therefore, the age-specific associations in different exposure windows and the associated mechanisms require further investigation.

The respiratory and cardiovascular system are particularly susceptible to air pollution (Yang et al., 2017). Therefore, pneumonia and CHD were selected for the disease-specific analyses. Consistent with the findings of previous studies (Negrisoli and Nascimento, 2013; Nhung et al., 2018; Santus et al., 2012), significant positive associations were observed for NO_2. Moreover, the pneumonia-related associations of NO_2 were stronger than those observed for overall death.

Surprisingly, O_3 was negatively associated with pneumonia-related death. In addition, this significant negative association remained stable after adjusting for other pollutants and performing the sensitivity analyses. In line with our findings, two studies conducted in Brazil found that a 10 μg/m^3 increase in the daily concentrations of O_3 was associated with a OR of 0.90 (95% CI 0.82-1.00) and 0.78 (95% CI 0.61-1.00) in pneumonia-related hospital admissions, respectively (Negrisoli and Nascimento, 2013; Souza and Nascimento, 2016). In contrast, Winquist et al. reported a positive association between O_3 and pneumonia-related emergency visits among infants (Winquist et al., 2012). Indeed, low concentrations of O_3 possess bactericidal properties, which have been used in clinical therapy (Baysan et al., 2000; Nogales et al., 2016; Rowen, 2018). Furthermore, the concentration of O_3 was relatively low in Beijing. Additionally, we observed negative associations between CO and pneumonia-related death; however, these associations were not statistically significant. Nguyen et al. also found that CO was negatively related to admissions of infants due to bronchitis and asthma (Nhung et al., 2018) and was associated with shorter length of hospital stay (LOS) for children with lower-respiratory infection (Nhung et al., 2019). A previous toxicological study reported the anti-inflammatory effects of exogenous CO, owing to its bactericidal properties (Nobre et al., 2009). However, a number of studies observed positive associations of CO with admissions due to pneumonia (Barnett et al., 2005; Nhung et al., 2017; Santus et al., 2012). Instead of hospital admissions, the outcome in our study was pneumonia-related death, which is more stringent than the outcomes used in previous studies. Additionally, we examined the associations of monthly exposure, whereas O_3 and CO may mainly exert acute effects on health (Gharibi et al., 2018; Kurai et al., 2018; Li et al., 2018; Zu et al., 2017).Therefore, we conclude that the associations between O_3 and CO and respiratory diseases require further investigation.

Regarding CHD-related death, significant associations were observed for $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO, and the estimates were stronger than those observed for overall and pneumonia-related death. CHD tends to lead to heart failure (Lambert et al., 2015; Srivastava et al., 2018). Previous studies indicated that hospitalization due to heart failure or death was associated with increases in the concentrations of ambient air pollutants (Buteau et al., 2018; Hsieh et al., 2013; Shah et al., 2013). Exposure to air pollution has been associated with increased systemic blood pressure and vasoconstriction (Huang et al., 2012; Quinn et al., 2017; Yang et al., 2018). Together with

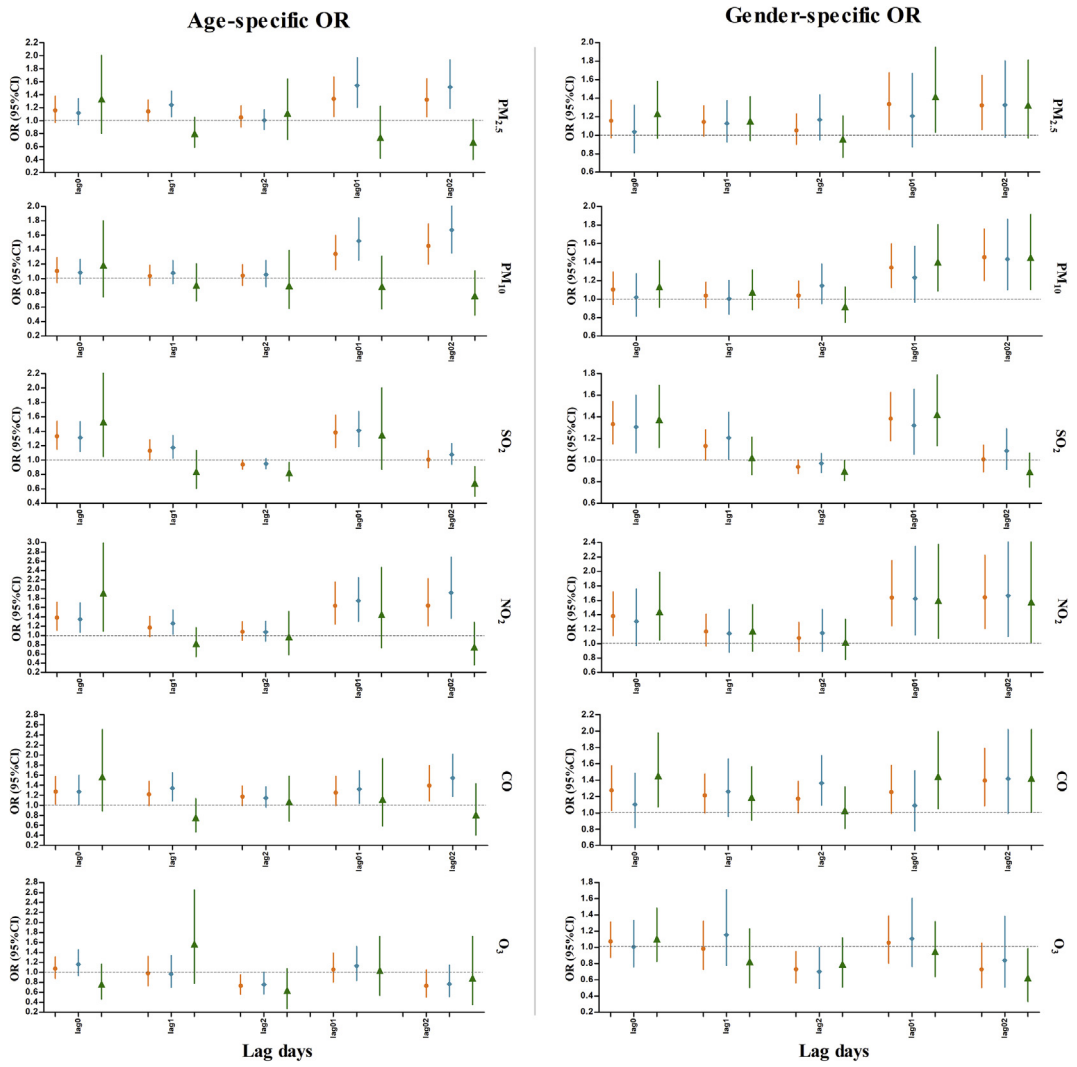


Fig. 4. Age- and gender-specific odds ratios with 95% confidence intervals per an interquartile range increase in the concentrations of air pollutants using different lag structures for overall death among children aged < 5 years in Beijing, China. *Age-specific OR: orange circles: overall children; blue diamonds: infants (< 1 year); green triangles: children aged 1–5 years. *Gender-specific OR: orange circles: overall children; blue diamonds: males; green triangles: females.

Table 3
Disease-specific odds ratios with 95% confidence intervals per an interquartile range increase in the concentrations of air pollutants using different lag structures for death due to pneumonia and congenital heart diseases among children aged < 5 years in Beijing, China.

Pollutant	Pollutant Lag0			Pollutant Lag1			Pollutant Lag2			Pollutant Lag01			Pollutant Lag02		
	OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI	
		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper		Lower	Upper
Pneumonia															
$PM_{2.5}$	1.171	0.572	2.398	0.957	0.580	1.578	1.217	0.671	2.208	0.935	0.412	2.122	0.933	0.422	2.062
PM_{10}	1.408	0.697	2.844	0.951	0.555	1.630	0.920	0.555	1.525	0.954	0.597	1.524	0.927	0.606	1.418
SO_2	1.592	0.931	2.722	0.839	0.548	1.283	0.998	0.770	1.295	0.951	0.510	1.772	0.975	0.618	1.538
NO_2	1.740[a]	1.057	2.865	0.736	0.335	1.620	1.230	0.609	2.486	1.433	0.468	4.385	0.621	0.209	1.847
CO	0.959	0.570	1.614	0.565	0.275	1.158	1.217	0.735	2.014	0.874	0.391	1.954	0.680	0.251	1.843
O_3	0.418[a]	0.237	0.738	1.269	0.310	5.195	0.772	0.339	1.762	0.455[a]	0.398	0.519	0.731	0.131	4.065
Congenital heart diseases															
$PM_{2.5}$	1.653[b]	1.083	2.523	1.086	0.780	1.511	0.671	0.418	1.076	1.691	0.884	3.236	1.123	0.644	1.960
PM_{10}	1.741[b]	1.085	2.796	1.008	0.737	1.378	0.948	0.623	1.442	1.281	0.765	2.145	1.086	0.656	1.799
SO_2	2.362[a]	1.594	3.500	1.409	0.951	2.089	0.800	0.537	1.190	2.479[a]	1.552	3.960	1.199	0.837	1.717
NO_2	2.103[b]	1.175	3.763	1.121	0.731	1.721	1.018	0.559	1.853	2.239[b]	1.043	4.806	1.732	0.809	3.706
CO	1.604[b]	1.058	2.433	1.047	0.650	1.686	0.882	0.523	1.490	1.540	0.725	3.271	1.013	0.521	1.967
O_3	1.036	0.593	1.809	1.311	0.613	2.804	0.935	0.445	1.967	1.240	0.599	2.565	0.975	0.547	1.735

*OR was estimated usin generalized additive Poisson regression, adjusted for time trends, season, year, holidays, temperature and relative humidity.
[a] $p < 0.01$.
[b] $p < 0.05$.

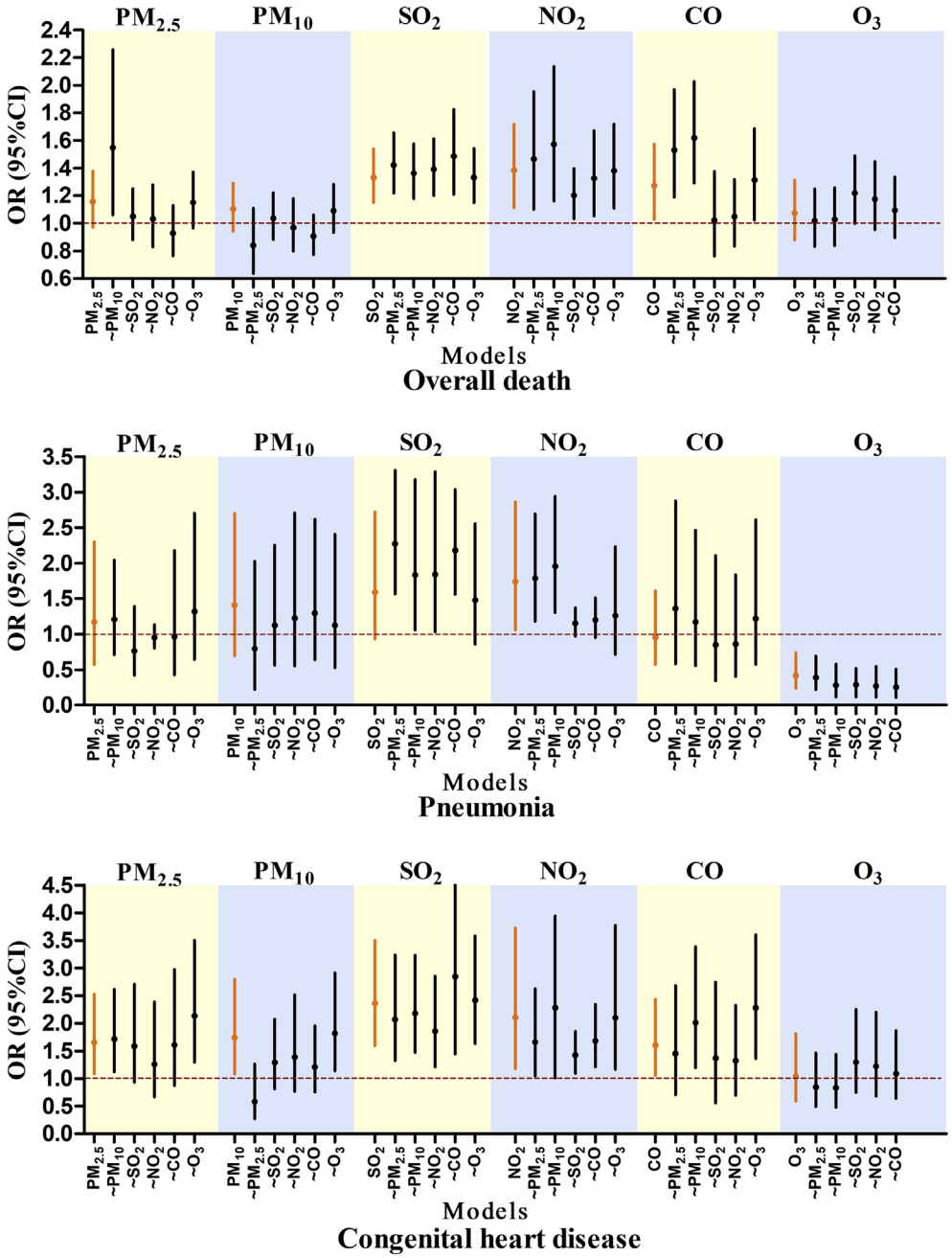


Fig. 5. Estimated odds ratios in the single- and two-pollutant models with adjustment for $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3 at lag0 for overall, pneumonia-related, and congenital heart disease-related death. *Orange circles: OR in single-pollutant models; black circles: OR in two-pollutant models.

arrhythmias, these associations of air pollution markedly increase the demands on the failing heart and thereby, potentially precipitate decompensation (Meo and Suraya, 2015). Moreover, infants with CHD tend to be preterm/low birth weight (Axelrod et al., 2016). Their regulatory and compensatory abilities are weaker than those of full-term infants. Based on this evidence, we conclude that children with CHD represent a susceptible population to ambient air pollution.

Two-pollutant models were implemented in our study to explore the possible role of single pollutants. One general observation was the tendency of PM_{10} estimates to decrease after adjusting for $PM_{2.5}$. All estimates of $PM_{2.5}$ were stronger after the inclusion of PM_{10}, especially for overall death, and the estimates of $PM_{2.5}$ at lag0 acquired statistical significance after adjusting for PM_{10}. These findings indicate that the estimates of PM_{10} were substantially explained by $PM_{2.5}$ indeed. Thus, we conclude that the associations between ambient particulate matters and the health of children are mainly due to $PM_{2.5}$. The SO_2 and NO_2 estimates (for overall death, pneumonia, and CHD) were the most stable across all two-pollutant models. Additionally, the estimates of $PM_{2.5}$, PM_{10} and CO decreased after the inclusion of SO_2 or NO_2, especially the estimates of CO, which lost statistical significance regarding its associations for both overall and CHD-related death. The SO_2 and NO_2 with CO models revealed the relatively independent associations of SO_2 and NO_2, whereas the associations of CO were substantially explained by SO_2 and NO_2 rather than CO indeed. Our findings were consistent with those reported in a previous study (Nhung et al., 2018). Therefore, we conclude that the associations of SO_2 and NO_2 on death may better reflect the associations between air pollution and death among children aged < 5 years in Beijing compared with other pollutants. Our study also contributes to the set of concentration-response functions one may use in NO_2-based health impact

assessments, following the recommendations of the WHO (Heroux et al., 2015).

There are several strengths in this study. Firstly, this was a population-based time series study; the mortality data were obtained from the Beijing Under-5 Mortality Rate Surveillance Network, which covers all children in Beijing, and the quality of the data was high. Secondly, Beijing has 35 air pollutant monitoring sites, which are located in both urban and suburban areas. Therefore, the levels of exposure were more representative. Other studies used only a few monitoring sites to estimate the levels of exposure in entire cities (Darrow et al., 2014; Liu et al., 2017; Negrisoli and Nascimento, 2013; Nhung et al., 2018). Thirdly, we considered monthly exposures to air pollution, which may capture sub-chronic associations.

Our study also had some limitations. Firstly, the sample size was limited, because the mortality among children aged < 5 years in Beijing were low (Cao et al., 2017). The monthly mean number of deaths among children aged < 5 years during the study period was 37.5. In addition, we were unable to investigate the specific associations between pollutants and SIDS due to the limited data. Secondly, seasonal stratified analyses were not performed due to the limited study period. However, we adjusted for seasonal variation in all models to control for bias. Thirdly, children who were alive for < 1 month were not excluded from the analysis. We conducted sensitivity analyses by excluding children who were alive for < 1 month, and the estimates were slightly lower than those of overall death. Therefore, the associations may have been overestimated. On the other hand, the estimated monthly mean exposures for children who were alive for < 1 month may also partly represent the exposures of their mothers. Previous studies reported that gestational exposures may also result in adverse birth outcomes, which are related to death in children (Lavigne et al., 2016; Smith et al., 2017). Finally, regional stratified analyses were not performed due to a deficiency in the residential information for each death case.

5. Conclusion

The results of this study suggest that exposure to ambient air pollution may account for increased deaths among children aged < 5 years in Beijing, China. NO_2 and SO_2 may be the most stable pollutants, reflecting the associations between air pollution and death. Children with CHD are more susceptible to air pollutants. Therefore, it is urgent to implement the clean air target values established by the WHO (Kutlar Joss et al., 2017) for the protection of children's health and reduction of their exposure to air pollution in Beijing.

Acknowledgements

We thank all healthcare workers in the Beijing Under-5 Mortality Rate Surveillance Network for their efforts in data collection. We thank the Beijing Environmental Monitoring Center and National Meteorological Information Center for providing us air quality and meteorological data.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envres.2019.108531.

Funding statement

This work was supported by The National Key Research and Development Program of China grant number 2016YFC0900603.

Conflicts of interest

There are no competing interests to declare.

Data sharing statement

No additional data are available.

Authors' contribution

Jing Wang, Han Cao: data collection, database establishment, statistical analysis and writing of the paper.

Dianqin Sun, Zifan Qi: data collection and database establishment.

Chunyue Guo, Wenjuan Peng, Yanyan Sun, Yunyi Xie, Xiaohui Liu, Bingxiao Li: database establishment.

Yanxia Luo, Ying Pan: modification of the paper.

Ling Zhang, Yichen Li: study design, data collection, direction of statistical analysis and writing and modification of the paper.

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