Letter to the Editor

Relationship between Short-term Exposure to PM$_{2.5}$ and Daily Lung Cancer Mortality in Nanjing[*]

WEI Fei Ran[1,&], XIONG Li Lin[2,&], LI Wei[3,&], WANG Xue Rong[4], HONG Xin[5], and CHEN Bao An[1,#]

Lung cancer is one of the most common types of cancer worldwide in terms of incidence, and it is the leading cause of cancer death. Many etiologic factors for lung cancer tumorigenesis have been identified to date, such as smoking and exposure to radon, cooking fumes, and asbestos[1]. A growing body of evidence indicates that particulate matter 2.5 (PM$_{2.5}$) is associated with lung cancer incidence[2]. Furthermore, PM$_{2.5}$ exposure after lung cancer diagnosis also shortens patient survival[3]. The health impacts of environmental PM$_{2.5}$ exposure may not manifest at the time of measurement, may be delayed, or may be prolonged. The distributed lag non-linear model (DLNM) has been frequently used in time series environmental health research, but it has seldom been applied to the evaluation of the relationship between short-term exposure to PM$_{2.5}$ and death from lung cancer. Thus, we performed a time-series study using DLNM to explore the correlation between relatively short-term exposure to PM$_{2.5}$ and the risk of lung cancer death in a Chinese population.

Daily mortality data from January 1, 2013, to December 31, 2017, were obtained from the Nanjing municipal center for disease control and prevention; the dependent variables were obtained from the 'China Disease Detection System Death Monitoring Network Report Database'. The data of the subjects including sex, age, permanent living address, date of death, and cause of death, were collected. According to the International classification of diseases 10th version (ICD-10) (http://apps.who.int/classifications/icd10/browse/2016/en), lung cancer was defined by the code ICD-10 C33–34. Daily mean air pollutant data on PM$_{2.5}$, sulfur dioxide (SO$_2$), carbon monoxide (CO), nitrogen dioxide (NO$_2$), and ozone (O$_3$) were obtained from Nanjing environmental monitoring center. Daily meteorological data including daily mean temperature, mean relative humidity, and mean air pressure were collected from the China meteorological sharing service system network (http://cdc.cma.gov.cn/home.do) during the same period as collection of the mortality data.

We established a fundamental model based on the DLNM to examine the non-linear lag influence of PM$_{2.5}$ on lung cancer deaths. Considering Y$_t$ to be the number of lung cancer deaths at day t following a Poisson distribution, in this study, the association of daily PM$_{2.5}$ with lung cancer mortality was estimated using generalized additive models (GAM) with quasi-Poisson regression, as follows: $Y_t \sim$ quasiPoisson (U_t), $\log(U_t) = \beta X_t + s$ (time, df) + s (temperature, df) + s (humidity, df) + s (air pressure, df) + s (windspeed, df) + (NO$_2$, df) + s (SO$_2$, df) + s (CO, df) + s (O$_3$, df) + HOD + DOW + α. In this study, 10 df per year for the time was used to control the long-term trend and seasonality of daily mortality[4], whereas dfs of temperature, relative humidity, air pressure, wind speed, NO$_2$, SO$_2$, CO, and O$_3$ were all defined as 3. The maximum lag days of air pollution were set as 7 days. The season was divided into warm (May to October) and cold (November to April).

During the study period, the number of lung cancer deaths in Nanjing was 14,693 with a daily average of 8.05. Among the individuals who died, 10,608 (72.20%) were men, and 85.12% (12,506/14,693) were older than 59 years. More than 75% (11,459/14,693) had a low educational level; peasants were predominant among the individuals who died (40.11%, 5,894/14,693), followed by

---

retired personnel (26.75%, 3,930/14,693) (Table 1).

The daily average level of $PM_{2.5}$ was 59.25 μg/m^3, with a range of 6.11–327.44 μg/m^3, which showed significant seasonal changes in characteristics. $PM_{2.5}$ was present at higher concentrations in cold seasons than in warm seasons. The number of days for which 24-h $PM_{2.5}$ (25 μg/m^3) exceeded Grade II CNAAQS (China National Environmental Quality Standards, 75 μg/m^3), Grade I (35 μg/m^3), and WHO guidelines was 462, 1,266, and 1,534 days, respectively. From 2013 to 2017, the number days for which the $PM_{2.5}$ concentration reached the WHO guideline standards were 16, 18, 54, 81, and 119 days respectively, which showed a trend of gradual increase.

With a reference value of 25 μg/m^3, the exposure-lag effect of $PM_{2.5}$ was highest at lag 0 day;

Table 1. General information about the study population

Variables	n	Percent (%)
Age groups		
< 45	213	1.45
45–59	1,974	13.43
> 59	12,506	85.12
Sex		
Male	10,608	72.20
Female	4,085	27.80
Year		
2013	2,815	19.16
2014	2,820	19.19
2015	2,928	19.93
2016	2,952	20.09
2017	3,178	21.63
Educational level		
College and above	1,078	7.34
High school/secondary school	1,869	12.72
Junior high school	11,459	77.99
Unknow	287	1.95
Occupational		
Professional and technical personnel	414	2.82
Staff/relevant personnel	572	3.89
Peasant	5,894	40.11
Worker	1,657	11.28
Retired personnel	3,930	26.75
Others	2,226	15.15
Total	14,693	100

as the lag days increased, the relative risks (RRs) decreased. When the lag was more than 4 days, the lag effect disappeared (Figure 1). The effect of $PM_{2.5}$ together with their 95% CI at the maximum value (327 μg/m^3), 99th percentile (196 μg/m^3), other percentiles (95th, 50th, 5th, 1th), Grade II CNAAQS (75 μg/m^3), and Grade I (35 μg/m^3) of $PM_{2.5}$ on lung cancer mortality risk along the lag days are shown in Figure 1. We found that the mortality caused by high concentration of $PM_{2.5}$ was more fluctuating during the lag period than that by its low concentration.

The overall cumulative effect of $PM_{2.5}$ is the sum effects of all the contributions of the exposure to the maximum lag indicated. The slice plot of the overall cumulative effect is presented in Supplementary Figure S1, available in www.besjournal.com; the relationship is represented as a linear curve without a threshold, and the risk of lung cancer mortality increases with a rise in the $PM_{2.5}$ concentration, with a significant difference.

At lag 0 to 4 days, with the average concentration of $PM_{2.5}$ increasing by 10 μg/m^3, $PM_{2.5}$ had a significant impact on the risk of lung cancer mortality all year round; at lag 0 day, the risk of lung cancer mortality for the population in Nanjing City increased by 0.69% (RR = 1.0069, 95% CI: 1.0021–1.0117, P < 0.05); at lag 0 day, the risk of lung cancer mortality increased to 0.58% (RR: 1.0058, 95% CI: 1.0001–1.0116, P < 0.05) during the winter season; the RR values for $PM_{2.5}$ was not significant during the warm season (Figure 2A). We used the moving average lagged model to estimate the cumulative effects of $PM_{2.5}$ on different season groups during lag days 0–7 (Figure 2B). The RR values showed an increasing trend from lag 0–1 to lag 0–7 all year round and in cold season; the cumulative effects reached its maximum on lag 0–7, the RR value was 1.0109 (95% CI: 1.0039–1.01179, P < 0.05) and 1.0113 (95% CI: 1.0028–1.0199, P < 0.05), respectively. However, the cumulative risk of $PM_{2.5}$ was not statistically significant during the warm season.

Clean air is considered to be a basic requirement of human health and well-being. However, air pollution continues to pose a significant threat to health worldwide. $PM_{2.5}$ is a severe air pollution problem in China, responsible for 1.1 million excess deaths in 2015. The daily average concentration of $PM_{2.5}$ in Nanjing is obviously higher than the WHO standard; the government should create regulatory policies to reduce the level of air pollutants. The daily average concentration of $PM_{2.5}$ of Nanjingis lower than that of Beijing, Jinan[5], and Lanzhou[6];
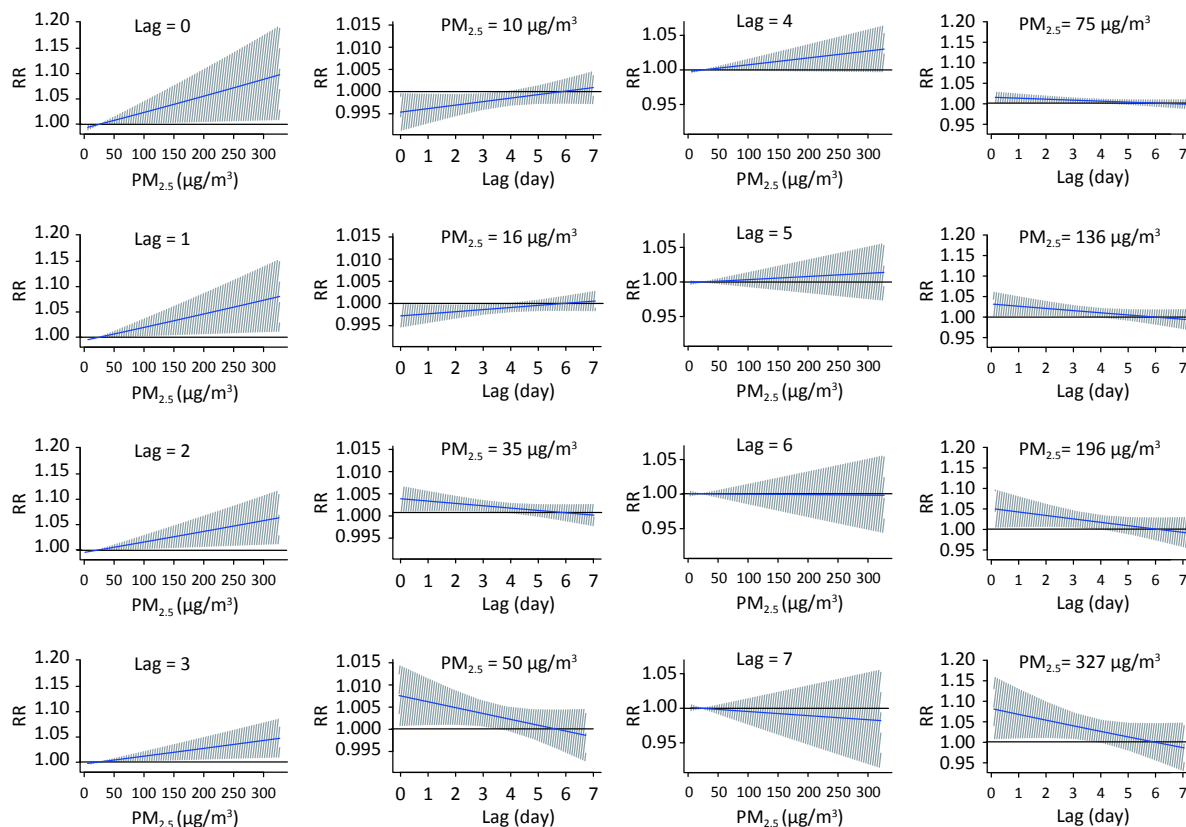
Figure 1. The exposure-lag-response relationship between PM$_{2.5}$ and lung cancer mortality.
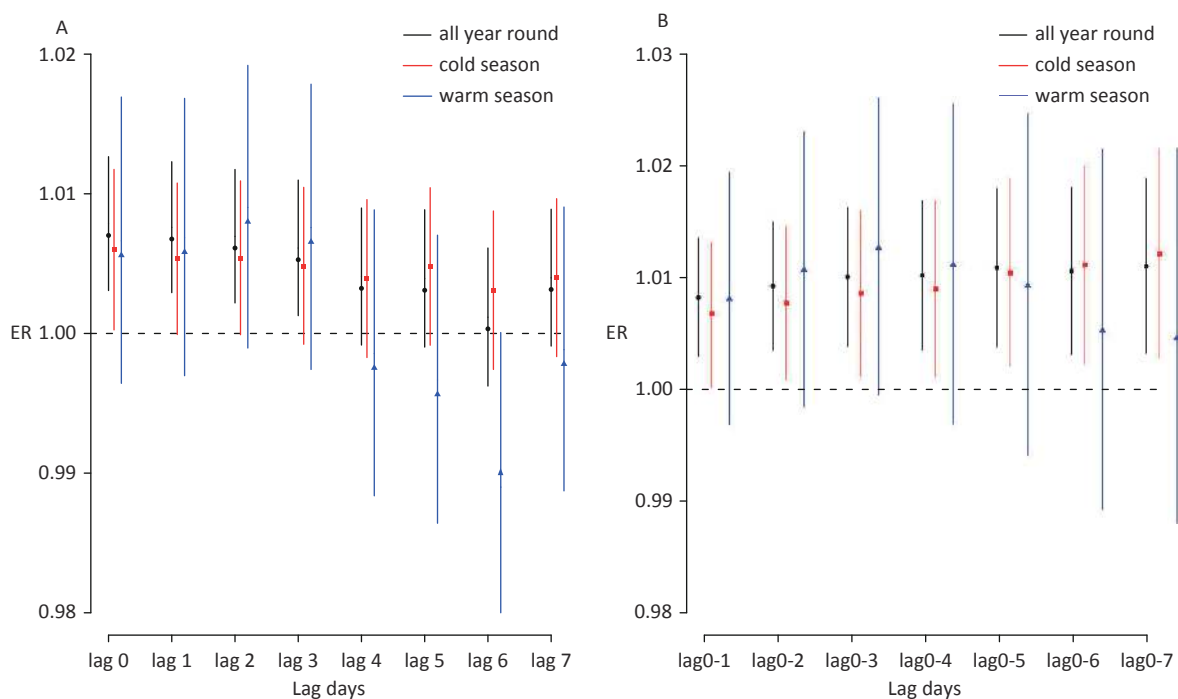

Figure 2. The excess risk of PM$_{2.5}$ on lung cancer mortality of different season groups.

the reason may be that northern cities provide heating in winter and spring, so that the average concentration in northern cities is higher than that in the south. The Chinese government has adopted a series of policies to control air pollution in recent years, and the average concentration of $PM_{2.5}$ in the air decreased nationwide. We found that the number of $PM_{2.5}$ compliance days showed a rising trend in Nanjing, and the WHO guildeline standard was reached for nearly one-third of the entire year of 2017. Most of the people who died of lung cancer in Nanjing were men, belonged to older age group, were farmers and retired people, and had low education levels; this is consistent with the findings of previous research[7]. It is suggested that targeted health education and promotion should be carried out for the high-risk groups of lung cancer.

We observed positive and significant associations of short-term $PM_{2.5}$ exposure with lung cancer mortality; single-day lag effects last for 3 days, then fade or disappear all year round. However, single-day lag effects showed a significant effect on lag 0 day during the cold season, while the warm season showed no significant effect. The reason may be that the concentration of $PM_{2.5}$ is higher in winter, where the toxic effects appear more quickly after exposure. Acute exposure to $PM_{2.5}$ induces a series of pathological changes in the lungs; induced oxidative stress could trigger autophagy in human lung epithelial A549 cells, which contributes to the impairment of pulmonary function[8]. The surface of $PM_{2.5}$ is rich in metallic elements, such as iron and copper, and harmful substances such as polycyclic aromatic hydrocarbons. It can lead to free radical peroxidation damage of lung cells, imbalance of intracellular calcium homeostasis, and inflammatory damage. $PM_{2.5}$ can penetrate deeply into the lungs, irritate and corrode the alveolar wall, and consequently impair lung function. The overall relationship between $PM_{2.5}$ and lung cancer death is positive and almost linear; this result suggests that there were no safe threshold effects or breakpoints, which is consistent with the findings of a previous study[9]. Both lag and cumulative effects are seasonal; the effect of the cold season is higher than that of the warm season. In the cold season, the average concentration of $PM_{2.5}$ increased significantly. Meanwhile, lung cancer patients with lobar bronchial obstruction and lobar atrophy are more likely to suffer, and the worst outcome of disease development is death.

There have been many studies on the correlation between $PM_{2.5}$ and morbidity/mortality of lung cancer. Long-term exposure to $PM_{2.5}$ is an important risk factor for lung cancer[10]; however, prior studies provide no information regarding the effect of short-term exposure on mortality. Our study has the following novelty. First, we use GAM to search for the relationship between lung cancer mortality and $PM_{2.5}$. The relationship between cancer mortality and contamination index is hysteretic, which can be better illustrated by the GAM model. Secondly, because there is a big difference in temperature in Nanjing in a single year, we focused on the effect of air pollution on lung cancer mortality in different seasons by stratified statistics. In brief, $PM_{2.5}$ obviously correlated with lung cancer mortality in Nanjing, China, and there was a significant increase in mortality associated with increased $PM_{2.5}$. Therefore, any reduction in pollutant concentrations will reduce the mortality of lung cancer. This study also suggests that the formulation of $PM_{2.5}$ standards should be stricter in China for public health. In our study, there were also some limitations. First, we only chose the data that came from Nanjing, so we did not investigate the association between lung cancer mortality and $PM_{2.5}$ in cities with better air quality. Second, our data were from 2013 to 2017, which is a relatively short period and might result in bias. Meanwhile, earlier air pollution warnings from the Chinese government would help the public to avoid outdoor activities, which leads to a drop in the saturation point, and furthermore, the maximum effect of $PM_{2.5}$ on lungcancer mortality may reduce.

The authors have no conflicts of interest to declare.

&These authors contributed equally to this work.

#Correspondence should be addressed to CHEN Bao An, Tel/Fax: 86-25-83272006, E-mail: cba8888@hotmail.com

REFERENCES

1. Shu Y, Zhu L, Yuan F, et al. Analysis of the relationship between $PM_{2.5}$ and lung cancer based on protein-protein interactions. Comb Chem High Throughput Screen, 2016; 19, 100–8.

2. Huang F, Pan B, Wu J, et al. Relationship between exposure to $PM_{2.5}$ and lung cancer incidence and mortality: A meta-analysis. Oncotarget, 2017; 8, 43322–31.

3. Eckel SP, Cockburn M, Shu YH, et al. Air pollution affects lung cancer survival. Thorax, 2016; 71, 891–8.

4. Gasparrini A, Scheipl F, Armstrong B, et al. A penalized framework for distributed lag non-linear models. Biometrics, 2017; 73, 938–48.

5. Liu Z, Liu Y, Zhang Y, et al. Effect of ambient temperature and its effect modifiers on bacillary dysentery in Jinan, China. Sci Total Environ, 2019; 650, 2980–6.

6. Chai G, He H, Sha Y, et al. Effect of PM$_{2.5}$ on daily outpatient visits for respiratory diseases in Lanzhou, China. Sci Total Environ, 2019; 649, 1563–72.

7. Yang J, Yin P, Zeng XY, et al. Lung cancer deaths attributable to ambient PM$_{2.5}$ exposure in 2016 in China. Chin J Epidemiol, 2019; 53, 475–9.

8. Xing YF, Xu YH, Shi MH, et al. The impact of PM$_{2.5}$ on the human respiratory system. J Thorac Dis, 2016; 8, E69–74.

9. Zuo B, Liu C, Chen R, et al. Associations between short-term exposure to fine particulate matter and acute exacerbation of asthma in Yancheng, China. Chemosphere, 2019; 237, 124497.

10. Fu J, Jiang D, Lin G, et al. An ecological analysis of PM$_{2.5}$ concentrations and lung cancer mortality rates in China. BMJ Open, 2015; 5, e009452.

GAM with default penalties
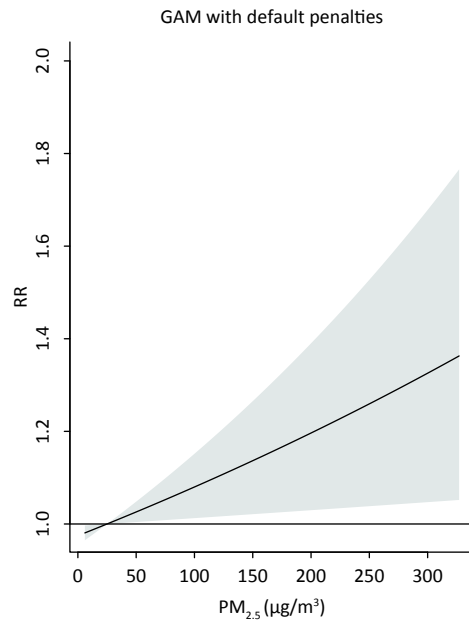
Supplementary Figure S1. The overall cumulative effect of $PM_{2.5}$ on lung cancer mortality.