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# Association of fine particulate matter on acute exacerbation of chronic obstructive pulmonary disease in Yancheng, China

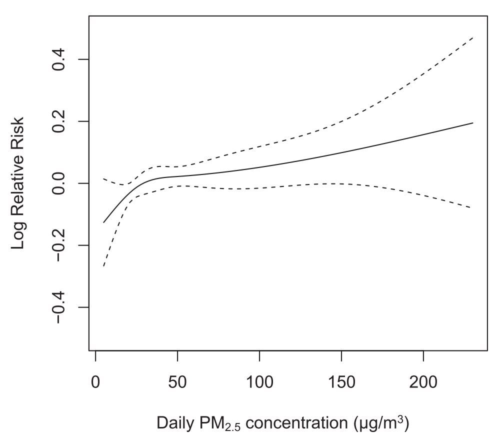
Qian Sun [a,1], Cong Liu [b,1], Renjie Chen [b], Can Wang [a], Jiading Li [c], Jian Sun [a], Haidong Kan [b], Jingyan Cao [c], Hongjian Bai [a,*]

[a] Department of Respiratory Medicine, the First People's Hospital of Yancheng, the Fourth Affiliated Hospital of Nantong University, Jiangsu Province 224006, China
[b] School of Public Health, Key Lab of Public Health Safety of the Ministry of Education, NHC Key Laboratory of Health Technology Assessment, Fudan University, Shanghai 200032, China
[c] Department of Cardiology, Yancheng Hospital Affiliated to Xuzhou Medical University and the First People's Hospital of Yancheng, Jiangsu Province 224006, China

## HIGHLIGHTS

- $PM_{2.5}$ was associated with an increased risk of acute exacerbation of COPD.
- Females and older COPD patients were more susceptible to $PM_{2.5}$.
- COPD patients were more sensitive to $PM_{2.5}$ in cold season.

## GRAPHICAL ABSTRACT

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## ABSTRACT

*Background:* Epidemiological evidence on the association between short-term exposure to fine particulate matter ($PM_{2.5}$) air pollution and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is limited in China.
*Objectives:* To explore the associations between $PM_{2.5}$ and AECOPD in Yancheng, China from 2015 to 2017.
*Methods:* In this time-series study, we used a generalized linear model with *quasi*-Poisson regression to investigate the association between $PM_{2.5}$ and AECOPD admitted in two major hospitals in Yancheng. We tested the robustness of the associations using two-pollutant models and examined the potential effect modification by age, gender and season via stratification analyses. Lastly, we fitted the concentration-response curves.
*Results:* We identified a total of 4761 AECOPD inpatients during the study period. The average daily-mean $PM_{2.5}$ concentration was 45.2 μg/m$^3$. Each 10 μg/m$^3$ increase in $PM_{2.5}$ concentration on the concurrent day of the onset of AECOPD was associated with a 1.05% (95% confidence interval: 0.14%, 1.96%) increase in AECOPD. The association was robust to the adjustment of ozone, but not to sulfur dioxide, nitrogen dioxide, and carbon monoxide. The association was larger in females, elderly patients, and was restricted within the cold season, but all between-group differences were insignificant. The concentration-response relationship curves were generally linear but flatted at concentrations over 40 μg/m$^3$.

* Corresponding author at: No. 166 Yulong West Road, Yancheng, 224006, China.
*E-mail address:* Bhj1066@139.com (H. Bai).
[1] These authors contributed equally to this work.

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*Conclusions:* This study demonstrated a higher risk of AECOPD associated with present-day $PM_{2.5}$ exposure in a Chinese city. We further provided important information on lag patterns, susceptible subgroups, sensitive seasons, as well as the characteristics of the concentration-response relationship curves.



## 1. Introduction

Chronic obstructive pulmonary disease (COPD), characterized by persistent respiratory symptoms and airflow limitation (GOLD, 2018), is a serious public health issue (Chen et al., 2016; Lopez-Campos et al., 2016; Thurston et al., 2017). According to statistics from the World Health Organization (WHO), COPD will become the third leading cause of death in the world by 2030 (Mathers and Loncar, 2006). China is a country with serious COPD disease burden. The Global Burden of Disease study reported that there were 54.8 million patients with COPD in China in 2013 (Yin et al., 2016). COPD patients frequently suffer acute exacerbations. The EPIC Asia study showed that nearly half of the patients with COPD had experienced exacerbations, 19% of which had been hospitalized (Lim et al., 2015). Frequent acute exacerbations of COPD (briefed as AECOPD), especially those requiring hospitalization, lead to impaired quality of life (Alahmari et al., 2014; Miravitlles, 2004), added economic burden to both society and family (Chen et al., 2016; Miravitlles et al., 2002) and increased mortality risk (GOLD, 2018).

Recent epidemiological studies have revealed that air pollution constituted an important risk factor for the development of COPD (Bloemsma et al., 2016; DeVries et al., 2017; Schikowski et al., 2014; Zhang et al., 2016). Among various air pollutants, fine particulate matter ($PM_{2.5}$) is believed to be most hazardous because it can easily reach the lower airways and carry many toxic components that trigger a variety of adverse responses (Fiordelisi et al., 2017; Nemmar et al., 2004). Epidemiological studies have indicated that short-term exposure to $PM_{2.5}$ was associated with increased risk of AECOPD (Li et al., 2016; Ni et al., 2015; Sun et al., 2018). However, most of these studies were conducted in Europe and North America, where the characteristics of population vulnerability, air pollution mixture, and exposure patterns may be apparently different from those in developing countries (Gan et al., 2013; Kloog et al., 2014; Samoli et al., 2014). As the largest developing country, China is facing one of the most severe air pollution problems. However, few studies have been conducted, especially those examining the association between $PM_{2.5}$ and AECOPD (Hwang et al., 2017; Sun et al., 2018). Therefore, we performed a time-series study to explore the association between $PM_{2.5}$ and AECOPD in Yancheng, one of the major cities in Jiangsu Province of China.

## 2. Materials and methods

### 2.1. Health data collection

Daily counts of AECOPD were obtained from Yancheng First People's Hospital and Third People's Hospital, which are the two largest hospitals in Yancheng City. They are both the largest general hospitals (also the top-level hospitals) in Yancheng City, which served >80% of the total patients and admitted almost all COPD patients resided in the urban areas of this city. We identified hospitalization for AECOPD using the 10th revision of International Classification of Diseases (ICD-10) codes (J44.100 and J44.101) over the study period from Jan 1st, 2015 to Dec 31th, 2017. The computerized medical record provided patient information including gender, age, admission and discharge dates and home addresses. The data on AECOPD was aggregated by the date of self-reported onset of AECOPD symptoms, rather than by the date of hospitalization based on the medical records of patients that were admitted to the two hospitals. We divided the daily counts of AECOPD into several strata by age ranges (≤65 years, 66–75 years and >75 years) and gender. The Ethics Committee of Yancheng First People's Hospital approved the study protocol.

### 2.2. Environmental data

Daily concentrations of criteria air pollutants during the study period, including $PM_{2.5}$, sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), carbon monoxide (CO) and ozone ($O_3$), were obtained from the Yancheng Environmental Monitoring Center. We calculated the 24 h average concentrations of air pollutants across the five monitoring stations in Yancheng to represent the daily exposure concentrations for all residents (Xu et al., 2016; Zhao et al., 2017). We excluded patients who lived >10-km away from the monitoring station. To allow for the adjustment of weather conditions, we obtained daily mean temperature and mean relative humidity from the Yancheng Meteorological Bureau.

### 2.3. Statistical analyses

Since daily hospitalization approximately follows a *quasi*-Poisson distribution, we used the over-dispersed generalized additive models (GAM) to examine the associations between $PM_{2.5}$ and hospitalizations for AECOPD. We adjusted for time-varying confounders based on previous studies (Liang et al., 2018; Qiu et al., 2012; Tian et al., 2016), including a natural smooth function of calendar day with 7 degree of freedom (*df*) per year, a natural smooth function of daily mean temperature of 4-day moving average with 6 *df*, a natural smooth function of the same-day relative humidity with 3 *df*, an indicator variable of day of the week (DOW) and a binary variable of public holidays. The formula for the main model is summarized as:

$$\text{Log}\,[E\,(Yt)] = \alpha + \beta * PM_{2.5} + NS\,(t, df = 7/\text{year}) + NS\,(\text{Temp}, df = 6) + NS\,(\text{Rh}, df = 3) + \text{holiday} + \text{DOW}.$$

where, Yt denotes the daily counts of AECOPD on day t; E(Yt) is the expected daily count on day t; t is the calendar time; β is the regression coefficient; *df* indicates the degrees of freedom; NS indicates the natural spline smooth function; and DOW is the day of week.

To explore the temporal pattern for the associations between $PM_{2.5}$ and AECOPD, we examined the associations using different lag periods, including the concurrent day of the onset of AECOPD (lag 0), the previous day (lag 1), the previous 2 day (lag 2), the 2-day average (lag 01) and the 3-day average (lag 02).

Furthermore, we performed additional analyses. First, we controlled for other four criteria air pollutants ($SO_2$, $NO_2$, CO, $O_3$) in two-pollutant models to test the robustness of the findings of $PM_{2.5}$. Second, we separately examined the associations between $PM_{2.5}$ and hospitalizations during warm season (May–October) and cold season (November–April) in the single-pollutant model. Third, we conducted stratification analyses to explore the potential effect modification by gender and age. We further evaluated the statistical significance for the differences in estimates across strata by calculating 95% confidence intervals (CI) as $(\hat{Q}1-\hat{Q}2) \pm 1.96\sqrt{S\hat{E}_1^2 + S\hat{E}_2^2}$, where $\hat{Q}1$ and $\hat{Q}2$ are the estimates for two categories, and $S\hat{E}_1^2$ and $S\hat{E}_2^2$ are their standard errors (Chen et al., 2012). Finally, we fitted the concentration-response relationship curves to get an overall shape of the association between $PM_{2.5}$ and AECOPD. We also conducted statistical tests to compare the difference between the linear model and smooth-spline model.