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Association between ambient air pollution and hospital admission for epilepsy in Eastern China

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ABSTRACT

Background: We aimed to study the short-term association between air pollutants and hospitalization for epilepsy in 47 hospitals from 10 cities in eastern China.
Method: We identified hospital epilepsy admissions in 2014 and 2015. A conditional Poisson regression model was used to examine the association between air pollutants and hospital admission, with temperature and relative humidity adjusted using the natural spline (ns) function. Pollutants included sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbon monoxide (CO), and particulate matter (PM). The association was stratified by sex, age, and geographic region in single-pollutant and two-pollutant models.
Results: An interquartile (IQR) increase of NO_2 and CO on the concurrent day is correlated with an increased admission of 2.0% (0.5%, 3.6%) and 1.1% (0.1%, 2.1%), respectively. The association is stronger in children (≤18 years) and in northern China, but did not vary with sex. A positive association was also observed on the previous day for CO [1.5%, 95% confidence interval (CI): 0.3%, 2.6%], NO_2 (2.5%, 95% CI: 0.6%, 4.3%), and $PM_{2.5}$ (1.32%, 95% CI: 0.16%, 2.48%). Moving average concentration of 7 days for all pollutants was associated with decreased admission (CO: -1.29%, NO_2: -0.4.69%, SO_2:-2.12%, $PM_{2.5}$:-0.98%, PM_{10}:-1.70%).
Conclusion: Exposures to NO_2 and CO on concurrent days, and $PM_{2.5}$ on the previous day, are associated with increased epilepsy hospitalization, whereas cumulative exposure appeared protective.

1. Introduction

Epilepsy is a common neurologic disease characterized by abnormal neuronal excitability (Song et al., 2017), manifested as unpredicted and recurrent seizures (Fisher et al., 2005). It is a wide-reaching and complex disease, affecting over 70 million people ranging from neonates to the elderly (Singh and Trevick, 2016). According to a systematic review and meta-analysis, the prevalence of epilepsy in China has increased by 259% from 1990 to 2015 (Song et al., 2017). The impact of epilepsy is not only limited to physical damage, but also could cause psychological problems and psychiatric impact (Berg et al., 2017; Coppola et al., 2016; Kwon and Park, 2014; Lang et al., 2018; Radovic et al., 2017). Moreover, compromise in quality of life (QoL) and extra burden on the caregivers were also observed in epilepsy patients (Fong et al., 2018; Gutierrez-Angel et al., 2018; Puka et al., 2018).

Ambient air pollution is one of the crucial factors regarding health impact and economic burden in China (Lin et al., 2017; Niu et al., 2017). As the largest developing country in the world, China has faced the worst air pollution in decades, mainly due to its rapid economic development (Li et al., 2015). In January 2013, a hazardous dense haze affected more than 800 million people in Beijing, bringing attention to the health impact of air pollution (Zhang et al., 2017). Although the Chinese government has taken a series of actions to control emission load (Ge et al., 2017), over 80% of the Chinese population are exposed

Abbreviations: ns, natural spline; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; PM, particulate matter; IQR, interquartile; QoL, quality of life; HSRs, hospitalization summary reports; ICD-10, international classification of diseases-10; AIC, akaike's information criterion; CI, confidence interval; CNS, central nervous system

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to pollution above the Interim Target-1 limit (35 μg/m^3) proposed by the World Health Organization (WHO) in 2016 (Niu et al., 2017). Air pollutants is comprised of gaseous pollutants and particulate matter (Bourdrel et al., 2017; Ning et al., 2018; Zhou et al., 2018). The health impact of both types of pollutants was broadly studied, especially the impact on cardiovascular disease (Bourdrel et al., 2017; Fuller et al., 2017; Khaniabadi et al., 2017; Vidale et al., 2017) and respiratory diseases (Mo et al., 2018; Nunes-Silva et al., 2017; Saygin et al., 2017; Vardoulakis and Osborne, 2018) in relation to mortality, outpatient visits, and hospitalization. However, the association with neurological diseases was insufficiently investigated. Xu et al. found that carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) were associated with increased outpatient visits for epilepsy based on a single-center study in China (Xu et al., 2016a). Before that, significant coefficients were also observed on epilepsy hospital admission in Chile (Cakmak et al., 2010). Moreover, all pollutants were observed to be associated with increased admissions, but the effect of each pollutant is inconsistent. In addition, neurotoxicity of the pollutants were also observed in controlled animal studies (Costa et al., 2014; Yun et al., 2013).

To the best of our knowledge, limited studies have been performed regarding the health impact of air pollutants on epilepsy. Thus, we conducted this study in 10 provincial capital cities in eastern China to provide clues for air pollutants as potential risk factors and inspire further exploration of the mechanism.

2. Material and methods

2.1. Study population

The data in the present study were extracted from the database of top grade 3 A hospitals' (tertiary hospitals) electronic hospitalization summary reports (HSRs) evaluated by the National Hospital Performance Evaluation Project conducted by the National Healthcare Data Center of China. The hospital infrastructure, medical service, management, technical level and efficiency, and quality and safety of clinical care were considered in the ranking system. The clinical information provided by HSR included the following: basic demographics, admission and discharge diagnoses in Chinese and corresponding International Classification of Diseases-10 (ICD-10) codes, discharge status (survival status, drug allergies, and hospital infections), surgical treatment, and financial costs.

We identified hospital admissions for epilepsy (ICD-10 codes G40 and G41) from January 1, 2014 to December 31, 2015 based on the admission diagnosis using ICD-10 codes. Chinese diagnoses were also checked to ensure the validity of diagnosis. In situations in which the daily admission a city was too few for a robust analysis, cities with total admission less than 1000 were excluded. In total, we identified 51,523 admissions from 10 large cities in eastern China, including 2 municipalities and 8 provincial capitals, as shown in Figure S1.

2.2. Air pollution and meteorological data

Air pollutants are comprised of gaseous pollutants and particulate matter (PM). Data on air pollution including PM less than 2.5 μm and 10 μm in aerodynamic diameter ($PM_{2.5,}$ PM_{10}), SO_2, NO_2, and CO between January 1, 2014 and December 31, 2015 were obtained from the National Air Pollution System. There are several ambient air-monitoring stations run by the Chinese government in each city to provide hourly data for the mandatory monitoring system. The daily mean concentrations of air pollutants were included in the present study. For adjustment of weather conditions, we obtained meteorological data [24-hour average temperature (°C) and relative humidity (%)] from the Chinese Meteorological Bureau based on its state-run observatories in each city.

2.3. Study design

We performed pooled analyses, for which observations for each city were combined. The association between air pollutants and admission was investigated by a time-stratified case-crossover study design. Each case serves as its own control by comparing exposure before and after the case period in the same city (Liu et al., 2017a). Thus, this design adjusts for individual time-invariant confounders (Oudin et al., 2018) and long-term trends(Liu et al., 2017a). In the present study, exposure was compared with the referent day matched on the day of the week within the same month.

2.4. Statistical analysis

Spearman's correlation tests were applied to examine the association between air pollution concentration and meteorological data. As risk of epilepsy and pollutants and weather data were based on a larger population, we assumed a Poisson distribution. The Poisson regression model served as a flexible alternative to conditional logistic regression when exposure was the same across individuals without expanding data and thus accelerating the computational process (Armstrong et al., 2014). We ran conditional Poisson regression models allowing for both over-dispersion and auto-correlation in the residuals.

Based on the published work, natural smooth (ns) functions of temperature and relative humidity were applied to adjust for a non-linear confounding effect of meteorological condition (Chen et al., 2016; Lee, 2012; Xu et al., 2016a). Based on the existing literature and result of Akaike's Information Criterion (AIC) tests for model fitness of present data (Table S1), 3 degrees of freedom were incorporated for the weather variable. We also incorporated public holidays in the model as a dummy variable. Lag effects were studied both as single-day lag (lag 0 to lag 7) and moving average (lag 02 lag 07) for accumulative influence. To avoid collinearity, concentrations of each pollutant first were included in the regression model separately. For sensitivity analysis, a two-pollutant regression model was also performed.

After establishing the basic model, we performed sex-, age-, and geographic-specific analyses. Next, we performed a lag effect model on each pollutant to explore deferred response. Besides the models mentioned, we tested whether the association was sensitive to adjustment of co-pollutants through two-pollutant models.

We considered $P < 0.05$ to be statistically significant. All statistical analyses were performed by STATA (version 12, Stata Corporation, Texas, USA). Unless specified otherwise, the pollutant effect was generally expressed as interquartile (IQR) increase of epilepsy admissions with an IQR increase [95% confidence intervals (CIs)].

3. Results

3.1. Demographic characteristics of epilepsy admissions

The mean age [standard deviation (SD)] of the patients was 16.91 (18.66) years. Of the total of 51,523 admissions, 30,908 (60.0%) patients were male, 35,446 (68.8%) were less than 18 years of age, and 20,820 (40.4%) were from southern China (Table 1).

3.2. Air pollution and meteorological variables

Table 2 shows the concentration of air pollutants and meteorological statistics in the 10 studied cities. The concentration of air pollutants were 48.2 ± 21.5 μg/m^3 for NO_2, 23.6 ± 29.9 μg/m^3 for SO_2, 1.1 ± 0.7 μg/m^3 for CO, 69.5 ± 57.5 μg/m^3 for $PM_{2.5}$, and 98.9 ± 68.6 μg/m^3 for PM_{10}, respectively. The temperature was 15.5 ± 10.7°C, and the relative humidity was 63.4% ± 19.8%). The means of air pollutants in northern China tend to be lower than those in southern China, whereas temperature and relative humidity vary inversely, but the difference was not significant.

Table 1
Demographic Characteristics of Epilepsy Admissions.

Variable	Numbers
Total	51523
Sex	
Male (%)	30,908(59.99)
Female (%)	20,615(40.01)
Age, y (mean ± SD) 16.91 ± 18.66	
≤18 (%)	35,446(68.80)
> 18 (%)	16,077(31.20)
Geographic Region	
Southern China (%)	20,820(40.41)
Northern China (%)	30,703(59.59)

The correlations between air pollutants and meteorological factors are presented in Table 3. The air pollutants are positively and significantly correlated with each other (r = 0.48-0.85, $P < 0.001$). Except for CO and $PM_{2.5}$ with temperature and CO with humidity, the pollutants are moderately and negatively (r = -0.59 to -0.05, $P < 0.001$) correlated with meteorological factors.

3.3. Concurrent effect of air pollutants

Table 4 summarizes the concurrent effect on epilepsy admissions for IQR increase of each positive pollutant, and a statistically significant association was observed in CO ($P < 0.05$) and NO_2 ($P < 0.05$), with an increase of 1.1% (95% CI: 0.1%, 2.1%) and 2.0% (95% CI: 0.5%, 3.6%), respectively. SO_2, $PM_{2.5}$, and PM_{10} tended to be positively associated with epilepsy hospitalization, but the association was not statistically significant. For sex-specific analysis, the association of either gender is not significant. The impact of pollutants on epilepsy admission is greater in younger patients (≤18 y) compared with adult patients (> 18 y), especially for CO and NO_2. The impact of pollutants in northern China of CO (1.3%, 95% CI: 0.3%, 2.3%) and NO_2 (2.4%, 95% CI: 0.4%, 4.3%) is more than that in southern China. Unexpectedly, hospital admission in southern China is significantly and negatively associated with CO (-3.9%, 95% CI −7.6%, −0.2%) and $PM_{2.5}$ (−3.4%, 95% CI −6.6%, −0.2%). The percentage change of epilepsy admission associated with a 10 $\mu g/m^3$ increase in air pollutant concentration is also provided (Table S2).

Table 5 shows the results of admission increase associated with IQR increase in CO, NO_2, and SO_2 in two-pollutant models. Compared with single-pollutant models, the association between CO, NO_2, and hospital admissions are stronger when adjusted for PM, with a 2.1% (95% CI: 0.7%, 3.5%) and 1.7% (95% CI: 0.3%, 3.2%) increase for CO, 3.8% (95% CI: 1.6%, 5.9%) and 2.9% (95% CI: 0.8%, 5.0%) for NO_2 when adjusted for $PM_{2.5}$ and PM_{10}, respectively. The coefficients of NO_2 in southern China (4.3% and 4.8%, respectively) were more than that in northern China (2.9% and 4.5%, respectively). An IQR increase in CO concentration was associated with a 2.4% (95% CI: 1.0%, 3.9%) and 1.7% (95% CI: 0.1%, 3.2%) increase in northern China, whereas the coefficients in southern China were not significant.

3.4. Lag effect and cumulative effect of air pollutants

There was a tendency that the single-day effect of air pollutants decreased over the lag days. The associations on the previous (lag 1) day for CO (1.5%, 95% CI: 0.3%, 2.6%), NO_2 (2.5%, 95% CI: 0.6%, 4.3%), and $PM_{2.5}$ (1.32, 95% CI: 0.16%, 2.48%) were positive and significant. The coefficient on lag 1 day for the remaining pollutants was positive but not significant. A negative association was observed from lag 4–7 days for CO and NO_2. Lag 5–7 for SO_2 and PM_{10}, and lag 6–7 for $PM_{2.5}$, also were negative and significant. For PM, the single-day coefficient on lag 1–3 tend to be stronger than that on the concurrent day. Moreover, the association on lag 1 day for $PM_{2.5}$ (1.3%, 95% CI: 0.2%, 2.5%) was significant.

The cumulative effect of 3 days for all pollutants tended to be positive, although not significant. In contrast, moving an average of 7 days for all pollutants was significantly negative (CO: -1.29%, NO_2: -0.4.69%, SO_2:-2.12%, $PM_{2.5}$:-0.98%, PM_{10}:-1.70%) (Figs. 1 and 2).

4. Discussion

To the best of our knowledge, this study is the third study of association between air pollutants and epilepsy worldwide, and the first multi-center study performed in large hospitals (grade IIIA in China, i.e., > 500 beds) in China. We obtained 51,523 admissions from 47 hospitals in 10 cities in eastern China. The target hospitals in the present study are all grade IIIA hospitals; therefore, the HSR data are of high accuracy. In the present study, NO_2 and CO were significantly related to the increase of epilepsy admission in both single-pollutant and two-pollutant models. The association is significant in patients

Table 2
Summary Statics for Air Pollutants and Meteorological Variables.

	Mean ± SD	Minimum	Percentile			Maximum	IQR
			25th	50th	75th		
NO_2, $\mu g/m^3$	48.2 ± 21.5	4.5	33.1	43.7	59.0	156.7	25.9
Southern China	44.5 ± 19	4.5	30.7	40.7	54.3	145.5	23.6
Northern China	50.7 ± 22.7	8.1	34.7	45.5	61.0	156.7	26.3
SO_2, $\mu g/m^3$	23.6 ± 29.9	2.0	8.0	14.5	26.9	334.9	18.9
Southern China	17.8 ± 10.9	2.0	11.0	15.0	21.5	106.5	10.5
Northern China	27.6 ± 37.2	2.0	5.6	13.7	33.5	334.9	27.9
CO, $\mu g/m^3$	1.1 ± 0.7	0.2	0.7	0.9	1.2	8.1	0.5
Southern China	0.9 ± 0.3	0.4	0.7	0.9	1.1	3.0	0.4
Northern China	1.2 ± 0.9	0.2	0.7	1.0	1.5	8.1	0.8
$PM_{2.5}$, $\mu g/m^3$	69.5 ± 57.5	5.2	31.3	53.7	88.2	897.5	56.9
Southern China	54.2 ± 35.9	5.8	29.0	45.6	69.0	543.5	40.0
Northern China	79.9 ± 66.4	5.2	33.9	61.9	105.4	897.5	71.5
PM_{10}, $\mu g/m^3$	98.9 ± 68.6	< 0.1	49.8	82.8	127.3	912.4	77.5
Southern China	77 ± 44.1	< 0.1	45.4	66.9	98.5	406.4	53.1
Northern China	113.7 ± 77.7	< 0.1	57.2	98.5	146.8	912.4	89.6
Temperature, °C	15.5 ± 10.7	−23.2	7.1	17.7	24.6	34.0	17.5
Southern China	18.5 ± 8.2	−2.0	11.9	20.2	25.4	33.5	13.5
Northern China	13.4 ± 11.6	−23.2	2.7	15.3	24.0	34.0	21.3
Relative Humidity, %	63.4 ± 19.8	8.0	50.0	67.0	79.0	100.0	29.0
Southern China	76.1 ± 12.4	21.0	69.0	78.0	85.0	100.0	16.0
Northern China	54.8 ± 19.3	8.0	40.0	55.0	70.0	100.0	30.0

Table 3
Spearman Correlation Coefficients between Air Pollutant Concentrations and Meteorological Statics.

	NO_2	SO_2	CO	$PM_{2.5}$	PM_{10}	Temperature	Humidity
NO_2	1.00						
SO_2	0.49***	1.00					
CO	0.70***	0.48***	1.00				
$PM_{2.5}$	0.67***	0.48***	0.78***	1.00			
PM_{10}	0.66***	0.54***	0.66***	0.85***	1.00		
Temperature	−0.37***	−0.59***	0.35***	0.34***	0.27***	1.00	
Humidity	−0.11***	−0.25***	0.06***	−0.05***	−0.27***	0.25	1.00

*** $P < 0.001$.

under 18 and in northern China. The correlation coefficient is not significant in either gender. Surprisingly, the concentration of CO is negatively correlated with epilepsy admissions, whereas the effect of NO_2 is not significant in southern China, suggesting that influence of the two pollutants might interact with other weather conditions, lifestyle factors, or other individual risk factors of epilepsy. The positive coefficients of CO and NO_2 were also confirmed in two-pollutant models.

Overall, an increase of only a few percentage points in admission was observed per pollutant quartile, which is consistent with the published studies. There were only two comparable studies prior to our study. One was conducted by Xu et al in Xi'an, a city in northern China. That study identified stronger significant positive effects of SO_2 and NO_2 on outpatient visits, with a 3.55% (95% CI: 1.93%, 5.18%) and 3.17% (95% CI: 1.41%, 4.93%) increase in relation to a 10 $\mu g/m^3$ increase of each pollutant, respectively. However, the effect of CO was statistically insignificant in their study. Besides, they found a significant protective effect of O_3 (Xu et al., 2016a). The other study was a nationwide study from 2001 to 2005 in Chile, which reported an adverse effect for each indicator in the present study. Although not significant, the point estimation of the coefficient of all pollutants on the concurrent and previous day in the present study tended to be positive. A seemingly stronger association is observed from October to April compared with the colder season in Chile (Cakmak et al., 2010), which suggests that the effect might alter with concentration levels of pollutants. The mean concentration of PM in Chile is less than one tenth of that in China, with NO_2 and SO_2 less than one thousandth. The exposure-response curve of PM might be steep at a low concentration and turn flat at a higher concentration. The exposure-response curve of gaseous pollutants (NO_2, SO_2, and O_3) showed a similar "steep-flat" profile in Xu's study (Xu et al., 2016a). In the present study, the warmer and more humid southern China is where hospital admission proved to be less positively (NO_2), and even negatively (CO), associated with pollutants in present study. This might suggest that the association between pollutants and epilepsy admissions might vary with climate. Meanwhile, disparities in race and health care services could not be ruled out when comparing the effect between countries.

As for lagged effect, CO, NO_2, and $PM_{2.5}$ level on the previous day was related to increased admission. The downward tendency over

Table 5
Percentage Change with 95% Confidence Interval Associated with IQR Increase in Air Pollutants (NO_2, SO_2, CO) in Two-pollutant Model.

	Adjust PM_{10}	Adjust $PM_{2.5}$
Overall		
CO	2.1(0.7, 3.5)**	1.7(0.3, 3.2)*
NO_2	3.8(1.6, 5.9)***	2.9(0.8, 5.0)**
SO_2	0.9(-0.5, 2.4)	0.7(-0.8, 2.1)
Northern China		
CO	2.4(1, 3.9)**	1.7(0.1, 3.2)*
NO_2	4.5(1.8, 7.3)**	2.9(0.2, 5.7)*
SO_2	0.8(-0.8, 2.3)	0.3(-1.2, 1.8)
Southern China		
CO	−3.9(-9.1, 1.2)	−2.1(-7.9, 3.7)
NO_2	4.8(1, 8.5)*	4.3(0.9, 7.8)*
SO_2	2.9(-3, 8.8)	3.5(-2.1, 9.1)

$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

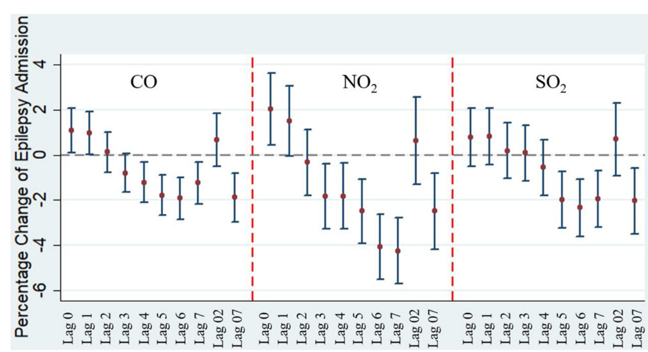

Fig. 1. Percent increase in daily admission for epilepsy associated with an IQR increase of gaseous air pollutants using different lag days in single-pollutant model. (Values were reported as means and 95% confidence intervals. Abbreviations: Abbreviations: Lag02 Lag07 stands for moving average of previous 2 and 7 days).

Table 4
Percentage Change (mean and 95% CI) in Epilepsy Hospitalization associated with IQR increase of Air Pollutants on the Concurrent Day in Single-pollutant Models.

Pollutants	CO	NO_2	SO_2	$PM_{2.5}$	PM_{10}
Overall	1.1(0.1,2.1)*	2.0(0.5,3.6)*	0.8(-0.5,2.1)	0.6(-0.7,1.9)	0.1(-1.3,1.5)
Sex					
Male	0.9(-0.3,2.2)	1.9(-0.2,3.9)	0.6(-1.1,2.3)	0.5(-1.1,2.2)	−0.4(-2.3,1.4)
Female	1.3(-0.3,2.8)	2.3(-0.2,4.8)	1.1(-0.9,3.1)	0.7(-1.3,2.8)	0.9(-1.3,3.2)
Age					
≤18	1.3(0.1,2.4)*	3.1(1.2,5.0)**	0.6(-0.9,2.1)	1(-0.5,2.5)	0.3(-1.4,2.0)
> 18	0.4(-1.6,2.4)	−0.5(-3.4,2.4)	1.2(-1.3,3.7)	−0.4(-2.8,2.1)	−0.2(-3,2.5)
Region					
Northern	1.3(0.3,2.3)*	2.4(0.4,4.3)*	0.7(-0.6,2.1)	1.4(-0.1,2.8)	0.4(-1.2,2.0)
Southern	−3.9(-7.6,-0.2)*	1.4(-1.3,4.2)	0(-4.5,4.6)	−3.4(-6.6,-0.2)*	−2.5(-6.1,1.1)

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

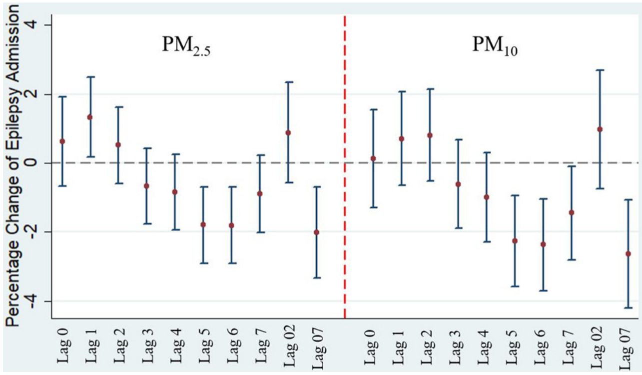

Fig. 2. Percent increase in daily admission for epilepsy associated with an IQR increase of particulate matter using different lag days in single-pollutant model. (Values were reported as means and 95% confidence intervals. Abbreviations: Lag02 Lag07 stands for moving average of previous 2 and 7 days).

lagged days for all pollutants was observed in the present study. For all indicators, the level on 4–5 days before admission and moving an average of the previous 7 days showed an unpredicted "protective effect." Moving an average of the previous 2 days tended to exert a positive effect, although it was not significant. A similar profile was seen in the Xi'an study in the 4–7 days before admission for NO_2. A negative coefficient on moving an average of the previous 7 days was seen in NO_2. Even though the "protective effect" is elusive, it seems that it is not random, since results are replicated in the present study. People might adapt their behavior, such as outdoor physical activities, according to heavy ambient air pollution attacks (Dong et al., 2018; Si and Cardinal, 2017; Yu et al., 2017), resulting in divergence between ambient pollution level and individual exposure. Which is to say that the negative coefficient did not necessarily indicate a "protective effect."

NO_2 is an essential component of automobile exhaust. Whereas a direct association between NO_2 and epilepsy is dubious. Sram et al. (2017) reviewed the role air pollution played in neurodevelopment based on several cohort studies. NO_2, as well as $PM_{2.5}$, significantly affected the central nervous system (CNS) in both children and adults. The association in children is relatively stronger in Spain, which is consistent with the present study. Wang et al. (2009) conducted a neurobehavioral study of traffic exhaust in two primary schools. Chronic exposure of NO_2, as well as other traffic exhaust, is observed to influence neurobehavioral function in school-age children. In animal models, NO_2 exposure influenced the CNS by altering triglyceride, free fatty acids, ganglioside, lipase activity, and lipid peroxidation. (Farahani and Hasan, 1990, 1992)

SO_2 is a well-recognized neurotoxic gaseous matter evidenced by a number of studies. Prenatal and postnatal exposure to SO_2 both affect the neurobehavioral development in early childhood (Chin et al., 2014). In 2013, Yun et al. (2013) discovered that inhaled SO_2 produced derivatives causing ischemic injury in young neurons and synaptic dysfunction in older neurons in rats. Others found that neuronal behaviors are also significantly influenced by chronic inhalation of SO_2 (Yao et al., 2015), which serves as indirect evidence of the correlation between SO_2 and childhood neurobehavioral development of prenatally exposed children (Chin et al., 2014). Moreover, SO_2 can also cause mitochondrial injuries in the mouse brain when co-exposed with $PM_{2.5}$ and NO_2 (Ku et al., 2016). Most recently, Niu et al found that endogenous SO_2 regulates hippocampal neuron apoptosis in developing epileptic rats and is associated with the PERK pathway.

CO binds to hemoglobin 230–270 times more avidly than oxygen, thus leading to formation of carboxyhemoglobin with subsequent reduction of tissue oxygenation (Varrassi et al., 2017). There is no direct evidence that CO intake through inhalation is related to increased frequency of epileptic seizure. However, in a recent rat model study, previously hypoxia-treated animals exhibited spontaneous recurrent seizures of increasing frequency within several weeks to 6 months after hypoxia without evidence of neuroanatomical injury (Justice and Sanchez, 2018). Further research is warranted on acute and chronic exposure of CO at ambient air pollution level and in real world populations.

Just like the other pollutants in the present study, direct evidence on PM was not found. Nevertheless, PM and its biological constituents may influence perturbations of blood-brain barrier integrity and systemic stress response (Liu et al., 2017b). Adverse neurologic effects also include oxidative stress, neuro-inflammation and brain immune interactions, (Costa et al., 2017) (Calderon-Garciduenas et al., 2013; Guerra et al., 2013), and nose-brain connection compromise in children (Lucchini et al., 2012). In controlled rat models, seasonal variation of PM_{10} caused ischemic-like damage in the rat brain (Guo et al., 2015).

Xu et al. (2016b) reviewed studies on pollutants and neurotoxicity. There were only four studies conducted on histological and biological effects of pollutants on human, perhaps due to the high cost on the complex procedure. Although evidence of acute neuro-inflammation was numerously found in animals, evidence in humans is limited and inconsistent. Cliff et al. (2016) conducted a research study on the acute effects of diesel exhaust exposure on CNS inflammation using quantitative electroencephalography (QEEG) and observed no significant effect on healthy adults. (Cliff et al., 2016) Whereas, volunteers in the controlled, blinded study that Cruts et al. (2008) conducted showed general cortical stress response. The aforementioned evidences suggest that ambient air pollutants might cause CNS disorder in healthy people. Studies of how air pollutants affect epilepsy patients are warranted. Our study has potential limitations. To begin with, the study is confined to provincial capital cities and tertiary hospitals located in the center of each city, leaving the association in smaller cities unclear. However, ambient air pollution is a nationwide problem in China, variation of pollutants in cities of different size is reported to be limited (Liu et al., 2017a). Secondly, we used the pollutant concentration levels as proxies of individual exposure level. This might cause underestimation of the exposure effect due to mismeasurement of the exposure (Goldman et al., 2011). Besides, we performed the two-pollutant model to test whether the correlation is robust. Considering the high correlation between pollutants, it is difficult to isolate the effects of different pollutants as in other published literature. Even though the regression coefficient is significant, the results should be interpreted with caution. Last but not least, all of the hospitals included in present study were tertiary hospitals. The results of the present study might reflect epilepsy admission displacement from secondary hospitals, indicating that epilepsy admission increases in the city might be greater than observed, and a decreased effect might be slighter. These factors might weaken the positive association between pollutants and admission.

There were certain strengths of this study. The database in the present study includes all grade IIIA hospitals, representing the top local hospitals. The hospitals included in our study all had a good reputation in diagnosis, medical education, coding, and on electronic HSR management. Beijing Municipal Health Bureau conducted a quality control study on HSR accuracy. The ICD coding accuracy of grade IIIA hospitals from 2006 to 2010 was over 95%. Moreover, we also double checked the narrative diagnosis in Chinese to ensure the precise identification of epilepsy admissions.

5. Conclusion

Short-term exposure to NO_2 and CO is associated with increased hospitalization for epilepsy. And, cumulative exposure of all pollutants in the present study appears to be a "protective factor." Future research regarding different levels of exposure to air pollution and epilepsy based on population and animal models are warranted.

Conflict of interests

Authors of the article report no conflict of interests

CRediT authorship contribution statement

Xiaoyuan Bao: Data curation, Formal analysis, Methodology, Writing - review & editing. **Xin Tian:** Data curation, Conceptualization, Formal analysis, Methodology, Writing - original draft. **Chao Yang:** Conceptualization, Writing - review & editing. **Yonghua Hu:** Writing - review & editing, Validation.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.02.012.

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