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Is the serious ambient air pollution associated with increased admissions for schizophrenia?

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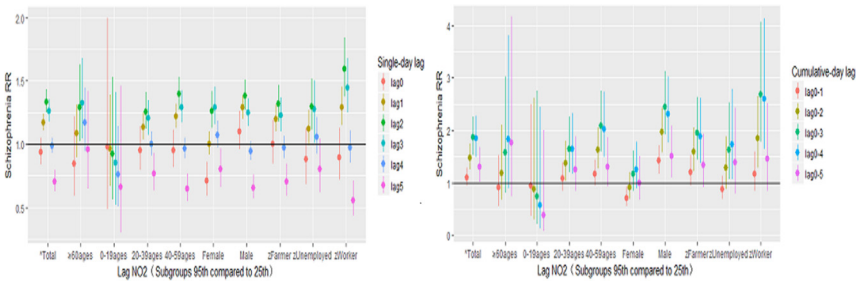
HIGHLIGHTS

- This was the first study to explore the relationship between NO_2, PM_{10}, SO_2 and schizophrenic admissions by using DLNM.
- NO_2, PM_{10} and SO_2 may increase the schizophrenic admissions.
- NO_2 and PM_{10} on schizophrenia presented a short-term effect, while SO_2 has longer effects.
- For high air pollution concentrations, male, 20-59 ages people, farmer and worker may be vulnerable people.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Much of the research has shown an increased risk of psychiatric disorders in association with elevated exposure to air pollution, such as NO_2, PM_{10} and SO_2. However, few studies investigate the effect of these air pollution on the risk of schizophrenia admissions and the lagged effect among different subgroups.
Methods: A distributed lag non-linear model (DLNM) combined with a Poisson generalized linear regression model was applied to analyzing the relationship between schizophrenia and air pollution. At first, according to the minimum AIC criterion, we discussed the lagged effect of NO_2, PM_{10} and SO_2 for 5 days, 4 days and 10 days, respectively. Then, we chose benchmarks as references (25th) to conduct comparisons with different levels of pollutant concentrations (90th and 95th). All patients were retrieved from the Psychiatric Hospital of TongLing (n = 3469) from January 2014 to December 2016. Daily air pollutants and meteorological data were collected from the Chinese national air quality monitoring (NAQM) and Meteorological Bureau. Subgroup analysis was conducted by gender (male and female), age (0–19 ages, 20–39 ages, 40–59 ages and ≥ 60 ages) and occupation (farmer, worker and unemployed).
Results: The effects of the three air pollutants were statistically significant to schizophrenia admissions. We found that NO_2 and PM_{10} have short-term effects of 4 days and 3 days (NO_2: lag 0–4 RR, 1.84(95% CI: 1.49–2.27), PM_{10}: lag 0–3 RR, 1.97(95%CI: 1.57–2.36)), respectively. SO_2 had longer effects for 10 days (SO_2: lag 0–10 RR, 2.93(95% CI: 2.10–4.10)). Additionally, it significantly increased the risk of schizophrenia episode in subjects with male, 20–59 ages, farmer and worker.
Conclusion: We find adverse effects of ambient air pollutants on schizophrenia admissions in TongLing, China, which may provide valuable information for the policy makers and local health authorities to conduct effective intervention of air pollution on schizophrenia.

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1. Introduction

The lifetime risk of schizophrenia is about 1%, associated with a large number of morbidity and mortality, as well as individual and social costs (Saha et al., 2007). It is an intricate, devitalizing, and clinically heterogeneous neurodevelopmental syndrome, closely linked to unstable functional damages in emotional, cognitive, and perceptual domains (Green and Glausier, 2016; Pagsberg, 2013; Owen et al., 2016). The editor of Nature magazine pointed that "schizophrenia is arguably the worst disease affecting mankind, even AIDS not excepted" (Listed, 1988).

The risk of schizophrenia is associated with the genetic and environmental factors, and there is increasing evidence showing that the environment has a significant impact on the genetic effect (Attademo et al., 2017). At the same time, the genetic risk is caused by a large number of alleles, including common alleles that might be detected by genome-wide association studies (Schizophrenia Working Group of the Psychiatric Genomics, 2014). However, high heredity has not translated into a satisfactory outcome of genetic disease (Insel, 2010), which potentially indicated environmental factors have become more and more considerable.

Currently, environmental pollution is a global problem with diverse and substantial public health implications. Quiet a few studies reported air pollution can cause systemic and neuroninflammation, neurodegenerative pathology, and cerebrovascular injury (Genc et al., 2012). Additionally, in the development process, brain toxicity of air pollutants is well recorded in both human and animal, and feasible biological pathways have been suggested (Ghorani-Azam et al., 2016). In recent decades, some epidemiological studies have found that exposure to air pollution (e.g. PM_{10}, SO_2 and NO_2) can lead to psychiatric disorders (e.g. depression, autism spectrum disorder (ASD) and any anxiety disorders) (Yang et al., 2017; Pun et al., 2017; Fordyce et al., 2017). But for schizophrenia, many environmental risk factors for schizophrenia have been identified. There was comparatively little research on air pollution as a possible risk factor. Through Spearman, a study in Israel showed that inhalation of air-suspended particulate can aggravate the risk of schizophrenia, and Lary et al. found that exposures to particulate matter were closely related to schizophrenia ($r = 0.61$, $p = 0.03$) (Lary et al., 2015; Yackerson et al., 2014). There was also a study indicating that NO_x has nothing to do with schizophrenia by using log-linear Poisson regression models (Pedersen et al., 2004). However, many studies indicated schizophrenia and autism also have common neuropathological characteristics, including ventriculomegaly and autism is said an early representative of schizophrenia (Allen et al., 2017; Shen et al., 2013). Additionally, mounting epidemiological studies have now connected components of pollutants to diagnosis of autism (Yang et al., 2017). A meta-analysis supported the hypothesis that exposure to NO_2, SO_2 and particles suspended matter were associated with an increased risk of autism (Flores-Pajot et al., 2016). So, we have reason to speculate "Is the ambient air pollution associated with increased admissions for schizophrenia?".

Therefore, in this study, we investigated the effect of major air pollution for schizophrenic admissions and explored the lagged effect of air pollution on schizophrenic episode among different subpopulation.

2. Materials and methods

2.1. Study sites and data collection

This study was conducted in TongLing, in eastern China. It has a typical subtropical climate, with four distinct seasons. The population of TongLing was about 1.712 million in an area of 3081 km^2 in 2016. Tongling is mainly coal as a fuel, rich in copper, accounting for 5% of the country, along with its pollution problems quite serious.

Daily statistics of patients with schizophrenia from January 1, 2014 to December 31, 2016 were collected from the Tongling Third People's Hospital. It is mental health center and is responsible for the mental disease prevention, rehabilitation and mental health guidance tasks in this region. All patients were hospitalized for acute schizophrenia, including data of gender, occupation, age and admission. The definition of schizophrenia is based on the international classification of diseases, 10th Reversion (ICD-10 codes: F20–F29). Before the cases of schizophrenia were collected, the ethics committee had been approved by the local ethics committee.

Meteorological data, such as mean temperature, relative humidity and sunlight were collected from the TongLing Meteorological Bureau. Data of air pollutants was retrieved from the NAQM stations of TongLing city. In particular, three principal air pollutants were contained (NO_2, PM_{10} and SO_2). There were few missing data in our study, with the rate of missing values: 0.1% for meteorogical data and 0.2% for pollutant data. So, we interpolated the missing values by using the mean of previous and the following days' values in process of data organization (Lavigne et al., 2014).

2.2. Data analysis

A Poisson generalized linear regression compared with DLNM was used to investigate the effect of air pollution on schizophrenia. Firstly, it is a general approach, which proposed to further relax the linearity assumption, and flexibly describe simultaneously non-linear and delayed effects. Secondly, it has statistical significance after the linear-nonlinearity test ($p < 0.05$). Thirdly, it showed non-linear effects of air pollution on schizophrenia admission. Single lag models were used to explore the association of schizophrenia visits with air pollution levels on the same day, one day, 2 days, or 3 days later to the day of a visit (described as lag 0, lag 1, lag 2, and lag 3). We also estimated the cumulative effect of air pollution with distributed lag models (defined as lag 0–1, lag 0–2, or lag 0–3). We calculated the lagged effect values of NO_2, PM_{10} and SO_2 for different days. Then, subgroup analysis was performed by occupation (farmer, worker and unemployed), age (0–19 ages, 20–39 ages, 40–59 ages and ≥60 ages), gender (male and female). For unemployed, because younger or older age groups might have been categorized into unemployed. We sifted out these people for unemployed (0–19 ages and ≥60 ages). Additionally, the relative risks of schizophrenia were calculated at high percentiles (90th and 95th) of daily air pollution compared with low percentile (25th), respectively.

According to the minimum AIC criterion, the lagged and non-linear effect of NO_2, PM_{10} and SO_2 for 5 days, 4 days and 10 days on schizophrenia, adjusted by sunlight and mean temperature for 7 days using the DLNM with the R package "dlnm". The effect of day of week (DOW) was controlled by using a categorical variable and the seasonality and long-term trend were controlled by introducing natural cubic spline of time with 8 degrees of freedom (df) per year.

Sensitivity analysis of the impact on model selection was made by time (6–8 df/year) and changes in pollutants (3–5 df). All statistical analysis used the R statistic software (version 3.1.1) and the "dlnm" package to fit the regression model (Gasparrini et al., 2010).

3. Results

3.1. Data description

In our study period, 3469 schizophrenia emergency admissions were included in our analysis. There were difference in gender, ages and occupations, with more cases male (2220 cases, 64.0%), 40–59 years (1771 cases, 51.1%) and farmer (1311 cases, 43.7%) (Table 1). The mean values of daily NO_2, PM_{10}, SO_2, temperature and sunlight were 37.6 $\mu g/m^3$, 90.0 $\mu g/m^3$, 48.2 $\mu g/m^3$, 16.5 °C and 5.6 h, respectively. Summary statistics for meteorological factors and air pollutant variables were described in Table 2.

Our study computed the Spearman correlations between pollutants and climate factors (Supplementary Fig. S1).