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Ambient sulfur dioxide levels associated with reduced risk of initial outpatient visits for tuberculosis: A population based time series analysis☆

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ABSTRACT

Background: Recent biochemical studies suggest that exogenous sulfur dioxide (SO_2) at low concentrations may have been beneficial in inhibiting *mycobacteria tuberculosis* (TB) growth. However, there is a dearth of population-based studies.

Objectives: To examine the association of ambient SO_2 levels and initial TB outpatient visits.

Methods: In Ningbo, China, we collected all daily initial outpatient visits for TB and routinely air pollution monitoring data between January 2009 and December 2013. A time-series study was conducted by using generalized additive regression (GAM) with log-linear Poisson models to estimate the associations between daily initial TB outpatient visits and daily average concentration of SO_2. Other traffic-related co-pollutants were adjusted. Sensitivity analyses were conducted to examine the relationship when 1% extreme SO_2 concentrations excluded or if related to the early onsets of TB symptoms.

Results: SO_2 concentrations in Ningbo were low with a daily average of 25 $\mu g/m^3$ (i.e. 0.0089 ppm). Negative associations were identified between ambient SO_2 concentrations and daily initial TB outpatient visits. A 10 $\mu g/m^3$ increase in SO_2 at lag_3 and $lag_{0\text{-}3}$ days were associated with −2.0% (95% CI, −3.2, −0.8) and −4.6% (95%CI, −6.8, −2.4) changes, respectively, in initial TB outpatient visits according to single-pollutant models. The negative association became stronger when nitrogen dioxide (NO_2) or particulate matter with aerodynamic diameter less than 10 μm (PM_{10}) was adjusted in two-pollutant models. This association was higher in males vs. females and in middle-aged adults vs. the elderly. We found a stronger negative association between SO_2 concentration and the initial symptom occurrence.

Conclusion: Short-term exposure to ambient SO_2 was associated with reduced risk of initial TB outpatient visits, suggesting acute protective effects of low-level ambient SO_2 exposure on bacteria-induced pulmonary infections.

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1. Introduction

Sulfur dioxide (SO_2) at room temperature is a non-flammable, colorless gas with a strong pungent odor. It easily dissolves in water and is primarily released from the combustion of sulfur-containing fossil fuels at power plants (73%) and other industry facilities (20%). Inhaled SO_2 readily reacts with the moisture of mucous membrane in upper airway to form hydrogen, sulfite, bisulfite, and sulfurous acid (H_2SO_3), all of which are severe respiratory irritation. Long-term exposure to elevated SO_2 concentrations, e.g. in 0.4~3 ppm, has been found to produce damage to airway epithelium, inhibit mucociliary transport, increase airway resistance, exacerbate asthma-like symptoms, and lead to bronchoconstriction (U.S. DoHaHS, 1998). Short-term exposures to ambient SO_2 have been epidemiologically linked with increased respiratory mortality and morbidity (Kan et al., 2010). However, findings of early epidemiological studies have been inconsistent, a phenomenon that may be due, in part, to heterogeneity of SO_2 concentrations and their impacts on geographically distinct populations (Wong et al., 2006). For example, Wong and colleagues found that daily variations of SO_2 concentrations were significantly associated with an increased risk of hospital admissions for respiratory diseases in Hong Kong, whereas in London this association was highly attenuated and insignificant after adjustment of other co-pollutants (Wong et al., 2002).

SO_2 is a preservative to prevent foods from rotting and has routinely served as an antibiotic and antioxidant in wine making (Wedzicha, 1984). The antimicrobial effect of SO_2 is caused by its ability to enter the cell membrane of a microbe and disrupt the activity of cells' enzymes and proteins, effectively inhibiting microbial growth (U.S. DoHaHS, 1998). Recent studies found that endogenous SO_2 has a physiological role on the regulation of pulmonary and cardiovascular function at physiological concentrations (Ma et al., 2012). A previous in vitro study suggested that exogenous SO_2 contributes to the inhibition of *mycobacterium tuberculosis* (*M.tb*) growth, which could be used to develop new medications to tackle multidrug resistant *M.tb* (Malwal et al., 2012). Tuberculosis (TB), an infection by *M.tb,* has been associated with the second largest mortality toll globally with an estimate of 9 million cases and 1.5 million deaths each year (WHO, 2015). High levels of ambient air pollution have recently been linked with risk for development of active TB (Smith et al., 2014; Jassal et al., 2013; Chen et al., 2016). Shilova et al. reported that atmospheric pollutants were associated with TB incidence in Russia (Shilova and Glumnaia, 2004). A previous study found that an interquartile increase in SO_2 concentration was associated with 7% increased TB incidence in Seoul, 1997–2006 (Hwang et al., 2014). However, recent epidemiological studies have shown no significant associations between TB and SO_2 in the greater San Francisco, Oakland, San Jose, Sacramento, and Fresno areas, northern California (Smith et al., 2016) and Taiwan (Lai et al., 2016). The effect estimates for TB associated with SO_2 have shown inconsistent. Our study hypothesized that low-level exogenous SO_2, in contrast to its toxicological effects at high-levels of exposure, may have protective effects on the development and/or progression of symptomatic TB.

Ningbo is the largest and busiest seaport in the world in terms of its cargo tonnage and volumes of incoming and outgoing freights. The outdoor emissions of SO_2 in Ningbo arise from shipping and motor vehicles, but this source has declined recently due to the use of cleaner low sulfur fuels and new technology for emission controls on public vehicles (China Ministry of Environmental Protection, 2010). In 2009–2013, the 24-h daily average concentration of outdoor SO_2 was 25 $\mu g/m^3$, significantly lower than that of Beijing (41 $\mu g/m^3$), Shanghai (56 $\mu g/m^3$), Xi'an (48 $\mu g/m^3$), Guangzhou (51 $\mu g/m^3$), Urumqi (100 $\mu g/m^3$), and most cities in China (Chen et al., 2012). The low-level SO_2 may also relate to seawater that has strong capacity of desulturization (Caiazzo et al., 2012). Ningbo, like Hong Kong (13.2 $\mu g/m^3$) and Bangkok (17.8 $\mu g/m^3$), is a coast city in East China (Fig. 1) (Kan et al., 2010).

Although the antimicrobial effects of SO_2 have been extensively reviewed in the literature (Kouokam et al., 2002; Zhao et al., 2016), there is no population data regarding its health effects on infectious diseases. We conducted a time-series study to examine the association between short-term exposure to ambient SO_2 and the risk of outpatient visits for TB in Ningbo, China.

2. Methods

2.1. TB reporting data

TB is a notifiable disease in China. The country implements an online national infectious disease reporting system that has documented patient demographic information, home address, diagnosis and his/her initial outpatient visit for TB related symptom in any health facilities (Wang et al., 2010). We obtained all TB case reports in Ningbo from the Zhejiang Provincial Center for Disease Control and Prevention (Zhejiang CDC) between 1st January 2009 and 31st December 2013. We collected information regarding patient's gender, age, current home address, names of the hospital for TB diagnosis and/or treatment, date of the initial onset of TB-related symptoms (such as persistent cough, low fever, or weight loss), date of the initial outpatient visit for TB, date of referring to TB designated hospital, laboratory test results, and whether the patient had multi-drug resistant TB. We used both the date of early symptom onsets and the date of the initial outpatient visits for TB as two different time indices to construct daily time series analyses. We included TB symptoms as persistent cough (coughing over consecutive two weeks), low fever, chest pain, weight loss, or sweating at night, as defined by the International Standards of TB Care (TB CARE I, 2014).

2.2. Pollutant and meteorology data

Air pollutant data were obtained from the Ningbo Environmental Monitoring Center for the same study period. The center has continuously collected data on pollutants from 18 fixed monitoring stations since the 1980s and included two more stations recently in the surveillance of six basic air pollutants, including SO_2, NO_2, CO, O_3, PM_{10}, and $PM_{2.5}$. The core area of Ningbo with the highest population density (12, 721 people/km^2) includes three primary and three secondary communities. The city-wide daily concentrations of SO_2 were estimated by averaging the 13 air monitoring stations within the core area of Ningbo (Fig. 1). The 13 stations, either sited in schools or on the roofs of buildings, represent the urban background concentrations of the city. Meteorological data on daily average temperature and relative humidity were obtained from the China Meteorological Data Center (http://data.cma.gov.cn) for the same study period.

2.3. Statistical model

In this study, generalized additive Poisson regression models were used to fit the relationship between the citywide daily SO_2 concentrations and the TB outpatient visits. In our analyses, partial autocorrelation function (PACF) was used to determine the degrees of freedom (*df*) for time trend, temperature, and relative humidity, respectively. The *df* was determined by the minimal absolute sum of PACF regarding day lags from 0 to 30 (Peng et al., 2006), In this way, 3 *df* per year was determined for time trend in the basic model excluding air pollution and weather variables. Residuals of the basic