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

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Main findings

This study is the first to present significant associations between SO_2 exposure and reduced risk of initial outpatient visits for TB at the population level.

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 25μg/m^3 (i.e. 0.0089ppm). Negative associations were identified between ambient SO_2 concentrations and daily initial TB outpatient visits. A 10μg/m^3 increase in SO_2 at lag_3 and lag_{0-3} 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 10μm (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.

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 0.4~3ppm, has been found to produce damage to airway epithelium, inhibit mucociliary transport, increase airway resistance, exacerbate asthma-like symptoms, and lead to bronchoconstriction.[1] Short-term exposures to ambient SO_2 have been epidemiologically linked with increased respiratory mortality and morbidity.[2] 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.[3] 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.[4]

SO_2 is a preservative to prevent foods from rotting and has routinely served as an antibiotic and antioxidant in wine making.[5] 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.[1] Recent studies found that endogenous SO_2 has a physiological role on the regulation of pulmonary and cardiovascular function at physiological concentrations.[6] 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*[7]. 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[8]. High levels of ambient air pollution have recently been linked with risk for development of active TB.[9-11] Shilova et al. reported that atmospheric pollutants were associated with TB incidence in Russia.[12] A previous study found that an interquartile increase in SO_2 concentration was associated with 7% increased TB incidence in Seoul, 1997-2006.[13] 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 Califonia[14] and Taiwan.[15] 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.[16] In 2009-2013, the 24-hour daily average concentration of outdoor SO_2 was 25μg/m^3, significantly lower than that of Beijing (41 μg/m^3), Shanghai (56 μg/m^3), Xi'an (48 μg/m^3), Guangzhou (51 μg/m^3), Urumqi (100 μg/m^3), and most cities in China.[17] The low-level SO_2 may also relate to seawater that has strong capacity of desulturization.[18] Ningbo, like Hong Kong (13.2 μg/m^3) and Bangkok (17.8 μg/m^3), is a coast city in East China (Figure 1).[2]

Although the antimicrobial effects of SO_2 have been extensively reviewed in the literature,[19 20] 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.

Methods

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.[21] 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.[22]

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 (Figure 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.

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,[23] 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 model were examined through residual plots and PACF plots to check if there were discernable patterns and autocorrelation. After the basic model was established, pollutant and weather variables, including daily mean temperature and relative humidity, were added. The degrees of freedom were determined as 13 for the same-day and the average of lag 1 through 5-day temperatures and 12 for the same-day and the average of lag 1 through 5-day humidity. Day of week and public holidays were included in the model as dummy variables. Sensitivity analyses were conducted to assess the key findings with 1% extreme highest and lowest concentrations of SO_2 excluded. The analysis results with and without the extreme concentrations were compared to minimize the bias from uncertainty in the air pollutant data measured. In addition, we also compared the daily time series generated from initial outpatient visits and the onsets of early TB symptoms, respectively, to examine the robustness of the estimate associations.

In single-day lag models, we examined the same-day 0-, and through 1- to 5-day lag relationships. We also examined the smoothing average effects of the air pollutant from lag 0 to lag 5 day (referred to as lag_{05} hereafter). Traffic, especially shipping, is an important source of SO_2. Thus, we studied whether associations between SO_2 and TB outpatient visits were sensitive to the adjustment of traffic-related pollutants, particulate matter with aerodynamic diameter less than 10μm (PM_{10}) and nitrogen dioxide (NO_2), respectively, using two-pollutant models in which co-pollutants were included. Effects were estimated by gender (i.e. male and female) and two age-specific subgroups: adults (15-65 years old), and elderly (≥65), respectively. There were only 98 cases of childhood TB (< 15 years old), which did not afford adequate power to do any associated subgroup analyses. To justify the assumption of linearity between the logarithm of outpatient visits and pollutant concentrations, this study used a natural spline smoother to graphically examine the exposure-response function. The excess risk (ER) estimates were represented as the percent change in TB outpatient visits per 10μg/m^3 increase of SO_2 concentrations. Data were analyzed using the MGCV package in R (version 3.2.0) (www.r-project.org). The locations of air pollutant monitoring stations were mapped using ArcGIS (v.9.3) (www.arcgis.com). There was no missing data in the analysis.

Results

Table 1 showed descriptive statistics on pollutants, weather, and initial outpatient visits for TB. SO_2 concentrations were low during this study period with a daily average of 25μg/m^3, compared with other Chinese cities such as Shanghai (44.7μg/m^3, 2001-2004), Wuhan (39.2μg/m^3, 2001-2004; 52μg/m^3, 2003-2005), Guangzhou (50μg/m^3, 2007-2008), Nanjing (51μg/m^3, 2007-2010), and Xi'an (48μg/m^3, 2004-2008).[2] A total of 18,316 TB-confirmed cases were recorded through hospital outpatients from 1st January 2009 to 31st December 2013. The daily counts were 13 on average. There were 98 children and 2,613 elderly cases, accounting for only 0.5% and 14.3%, respectively, among all TB cases. The correlations between the daily average concentration of SO_2 and the other two pollutants, PM_{10} and NO_2, were 0.65 and 0.78, respectively. The concentration of SO_2 was negatively associated with the daily averages of temperature (ρ = -0.61) and relatively humidity (ρ = -0.26).

Table 2 showed the percent change in outpatient visits for TB per 10μg/m^3 increase in the concentrations of SO_2, NO_2, and PM_{10} at lag 0, 1, 2, and 3 days in single-pollutant and two-pollutant models. The first three columns were effect estimates for the single day of 0 up to 5, respectively. The effect estimates for SO_2 were negatively associated with the risk of initial TB outpatient visits for all the six single-day lags. The same day (i.e. lag 0) was related to the largest TB risk reduction. A 10μg/m^3 increase in the concentration of SO_2 was associated with a -3.8% (95% confidence interval, -5.5 to -2.0) change in the total initial TB outpatient visits at lag_{05} according to the single-pollutant model. The negative association became stronger after adjustment for NO_2 and PM_{10}, respectively, in the two-pollutant models. PM_{10} and NO_2 demonstrated negative associations with the initial outpatient visit for TB, but none were statistically significant.

The results based on the daily outpatient visits were comparable with those regarding the initial onsets of related symptoms. Similar results were generated using the two different types of time series for both SO_2 only and SO_2 with PM_{10} and NO_2 adjusted. Sensitivity analyses showed that the effect estimates of SO_2 were consistently robust to the exclusion of the extreme SO_2 concentrations after adjustment for seasonal trends, weather variability, calendar periodicity, and public holiday (Supplementary documents: Table S1& S2).

Figure 2 shows the percentage change in TB outpatient visits per 10μg/m^3 increase in SO_2 concentration at smoothing lags of 0-1 to 0-5 days in a single pollutant models and two-pollutant models with NO_2 and PM_{10} adjusted, respectively. The estimates of the smoothing-lag effects on TB outpatient visits were larger than those of the single-day lags. The effect estimated were stronger for SO_2 with NO_2 or PM_{10} adjusted. The ER associated with SO_2 at lag_{05} day for middle-aged adults, the elderly, males, and females were -4.7% (95% CI, -6.9, -2.4), -2.9% (95% CI, -9.1, 3.7), -5.1 (95% CI, -7.6, -2.6), and -3.4 (95% CI, -7.1, 0.5), respectively, after adjusting for PM_{10}. Compared with the outpatient visits, results generated from the time series of the early symptoms were stronger and statistically significant (Figure S1). Similar to the result of outpatient visits, the negative associations were stronger in males vs. females, and in middle-aged adults vs. the elderly for the early symptom onset (Figure S1).

Figure 3 showed the exposure-response curves for daily average SO_2 at lag_3 and lag_{03} days, respectively, and the risk of outpatient visits for TB in single-pollutant and two-pollutant models with NO_2 and PM_{10} adjusted. A natural spline smoother with 4 df was applied on the SO_2 concentration. The exposure-response curves were essentially linear at the ambient SO_2 levels of 20-40μg/m^3. Compared to the initial TB outpatient visits, the linear exposure-response curves were stronger when conducting time series analysis using the early onset of TB symptoms (Figure S2).

Discussion

This was the first population-based study of which we are aware that examined the specific association between ambient SO_2 and initial hospital outpatient visits for TB in a port city with relatively low SO_2 levels. We found a negative association between ambient SO_2 and initial outpatient visits for TB. The protective health effects of SO_2 estimated were stronger for males than for females, and stronger for middle-aged adults than the elderly, based on our time series analysis using the initial symptom onsets of TB. Children were excluded in the subgroup analysis due to the relatively small number of cases.

We adjusted for the potentially confounding factors of NO_2 and PM_{10} since the primary SO_2 source in Ningbo is shipping and traffic. The negative association between SO_2 and initial TB outpatient visits became stronger after controlling for NO_2 and PM_{10}. Some early studies showing adverse respiratory effects of SO_2 did not adjust for the confounding effects of co-pollutants.[13] In studies where co-pollutant effects were evaluated using multi-pollutant models, positive associations between SO_2 and respiratory outcomes became insignificant after NO_2 and PM_{10} were adjusted.[24] Recently, the U.S. Environmental Protection Agency reported a linkage between exposures to elevated SO_2 level with asthma aggravation and adverse respiratory symptoms. To date, few studies examined the associations between SO_2 and TB outpatient visits under the context of co-pollutants. Even with those that identified a positive association of SO_2 with respiratory mortality or morbidity, the effects were attenuated after adjustment of traffic-related pollutants, particularly NO_2[2] the estimated increase in asthma hospitalization associated with SO_2 was reduced by 4.35% (using 7 df per year approach) after adjusting for NO_2.[25]

We conducted time-series analysis to assess the association between SO_2 and initial TB outpatient visits and sensitivity analysis to examine the relationship consistent with the early onsets of TB symptoms. Two different date indices were included: the date of initial symptoms onset and the date of the initial outpatient visit to any health facilities. The effects estimated from the early symptom onset were stronger. This might be related to patient delays and diagnostic delays due to patients not seeking treatment when having symptoms, or seeing several doctors before their initial TB diagnosed. This has been well documented in health service studies of TB control.[26] In addition, unlike asthma exacerbation and acute upper respiratory infections, latency TB with no symptoms takes a longer period, ranging from weeks to months, or even years, to become active with TB-related symptoms such as persistent cough, low fever, chest pain, or sweating at night. The impacts on latent TB may not be observed due to the long time latency period and in-apparent symptoms. Compared to initial outpatient visit, symptom onsets responded more immediately to the increased level of SO_2. Therefore, time lags exist in between symptom onsets and initial outpatient visits. However, the dates of symptom onset were self-report which depends on the accuracy of memories and quality of clinical consultation. We identified ambient SO_2 significantly associated with the reduced risk of outpatient visits for TB. Of note is that by using exact consultation dates, the effect estimates we made might underestimate the true impact of SO_2 on TB.

The negative association of initial outpatient visits for TB was stronger in males than females with SO_2 exposure. different effects estimated may relate to the varying intake fractions in the subgroups. Intake fraction is the fraction of total emission that is inhaled by a receptor population. The average intake fraction of SO_2 within 50 km was 4.2 x 10^{-6} for industry emission in urban China.[27] Compared to females, the large vital capacity in males and higher exertion rates from working in jobs requiring labor (which, in turn, are associated with higher exposure to ambient air pollution) might have caused a difference in the reduction of TB risk between the two subgroups. The effect estimates for the elderly and females might be statistically significant if longer TB time series were involved in the analysis. However, regarding to the onset of initial symptoms for TB, the negative associations appeared stronger and more statistically significant in middle-aged adults than in elderly. As the largest population, adults between 15-65 years old in Ningbo have reached 78.6% in 2005 and experienced most of the overall intake fractions.[18] Another explanation is that elderly with chronic medical status may be more prone to be infected with the bacteria.

The short-term protective effects of SO_2 against TB are biologically plausible. *M.tb* is a facultative intracellular pathogen that infects primarily alveolar macrophages (AMs) to replicate and disseminate within its hosts.[28] The bacteria have unique cell surface rich in complex lipids, including mycolic acids, cord factor, and wax-D. These materials are pathogenic agents determining bacterium virulence.[29] The biological effects of SO_2 have recently been noted and reviewed.[30] Exogenous admission of SO_2, by SO_2-releasing molecules, induced oxidative damage to biomacromoleculates such as lipids, proteins, and DNA,[31] thus inhibiting/killing *M.tb.*[7] Inhaled 14mg/m^3 SO_2 increased tumor necrosis factor-α (TNF-α) and interlukin-6 (IL-6) levels in mice lung tissues,[32] which are two pro-inflammatory cytokines against *M.tb* through regulating the activity of other cytokines and chemokines, and generating and maintaining organized granulomas during early infections.[33] Kienast et al. reported that a 30-minute exposure to 12.5ppm SO_2 induced 62% AMs death and 63% decrease in the release of reactive oxygen species.[34] Macrophage apoptosis, also, effectively resists TB and its bacterial growth.[35] Despite a previous vitro study showing TNF-α decreases in human AMs after SO_2 exposures, the AMs were obtained from eight patients with bronchial carcinoma but five of them were ex-smokers.[34] Increased SO_2 level was thought to augment and heighten the inflammatory response in common infections, initially to clear the microbe in early infections.[30] The anti-inflammatory activity of SO_2 may have a further protective effect against respiratory infections, such as virus-induced pneumonia,[36] and even cardio-pulmonary diseases, such as lipopolysaccharide-induced acute lung injury.[6]

The dose-response curves of the protective effects in TB were essentially linear at the ambient SO_2 levels of 20~40μg/m^3, much lower than those administered in experimental investigations.[32] For TB cases that do not show immediate symptoms after activations, the smoothing average effects of SO_2 exposure can be more significant than those measured regarding on a single-day lag. It should be noted that the exposure duration in the current study was a continuous 24-hour exposure, whereas it has been usually around 15~50 minutes per day for experimental investigations. SO_2 exposure duration and frequency, actually, are among the many unanswered questions for the application of inhaled SO_2 as a therapeutic: whether intermittent exposure to low levels of SO_2 has the same efficacy as one time dosing at a higher SO_2 concentration; and whether the SO_2 dosing regimen should be tailored to different age- or gender-specific subpopulations. Integrating the experimental and the observational epidemiology data may help gain more insights into the biological effects of SO_2 at low levels.

This was an ecological study and thus cautions should be noted in inferring cause-effect relations between low-level SO_2 exposure and initial TB outpatient visits. TB is a chronic disease, unlike acute infectious diseases that may result in immediate respiratory symptoms when infected. We used dates of the first visits to consultants in any health facilities for the estimate of SO_2 effects on TB developments. Such date index might include time lags between the initial symptom onsets and seeking diagnosis from hospital consultants. Although the effects might be underestimated using the initial outpatient date index, it warrants caution in the interpretation of negative associations between environmental SO_2 and TB. Whether SO_2 prevents the development of or lessens the severity of TB is difficult to judge. Some exposure misclassification was also likely due to the fact that SO_2 concentrations are usually heterogeneous in space and the limited number of fixed monitoring stations might not be representative enough for characterizing general population exposures. Moreover, the effect of long-term exposures to SO_2 on TB remains unknown. In this study, we applied time-series analysis to examine the daily variation of TB outpatient visits in relation to ambient SO_2 concentrations. The current study design only allows us to infer about the acute effects but the long-term effects require other epidemiological designs, such as cohort or case-control studies. The acute and chronic effects of SO_2 have been observed on cardiopulmonary system. Although acute exposure to low SO_2 levels may be regarded as potentially beneficial and cardiopulmonary protective, long-term exposures have been shown to be deleterious for cardio-respiratory health.[37] [38] Further studies are needed to evaluate the overall health effects of exposures to low-level environmental SO_2.

In conclusion, we found that low-level ambient SO_2 is associated with reduced risk of daily initial outpatient visits for TB. Caution should be noted in interpreting cause-effect relations due to the ecological design of this study. Findings on the short-term protective effects of SO_2 on initial TB outpatient visits need to be assessed together with other sources of evidence for the better understanding of the health effects of SO_2 at environmentally relevant levels.

Tables.

Table 1. Summary statistics of pollution, weather, and health data for Ningbo, 2009-2013.

Table 2. Percentage change (excess risk % with 95% confidence intervals) in total hospital outpatients for tuberculosis per 10 $\mu g/m^3$ increase in the concentrations of SO_2, NO_2, and PM_{10} at lag 0, 1, 2, 3, 4, and 5 days in single-pollutant and two-pollutant models.

Figure Legend

Figure 1. Ningbo city and the locations of air monitoring stations. The 13 air-monitoring stations within the black dash line were included for the city-wide average estimate of air pollutants' concentrations.

Figure 2. Percentage change in hospital outpatients for tuberculosis per 10 $\mu g/m^3$ increase in SO_2 concentration at moving average of 0-1 to 0-5 and the same days in single-pollutant and two-pollutant models with adjustment for NO_2 and PM_{10},

respectively. The results using adults and elderly, and males and females TB outpatient data were compared. The points indicate central estimates and vertical lines indicate 95% confidence intervals.

Figure 3. Exposure-response curves for daily average SO_2 at lag_3 and lag_{03} days and risks of outpatient visits for tuberculosis in single-pollutant and two-pollutant models with adjustment for NO_2 or PM_{10}. A natural spline smoother with 4 df was applied on the SO_2 concentration. The solid line represents central estimates and the envelopes represent 95% confidence intervals. Supplementary materials

Table S1. Summary statistics of weather, TB outpatients, and air pollution with 1% extreme values excluded.

Table S2. Percentage change (excess risk with 95% confidence interval) in outpatient visits for TB per 10 μg/m^3 increase in the concentration of SO_2 at lag 0, 1, 2, 3, 4, and 5 in single-pollutant and two-pollutant models. The effect estimates of daily average SO_2 with 1% extreme concentration excluded in GAM models after adjustment for time trends, weather conditions, public holidays, and days of weeks. The effect estimates of daily average SO_2 with 1% extreme concentration excluded in GAM models after adjustment for time trends, weather conditions, public holidays, and days of weeks.

Figure S1. Percentage change in early onsets of tuberculosis symptoms per 10 μg/m^3 increase in SO_2 concentration at moving average of 0-1 to 0-5 and the same days in single-pollutant and two-pollutant models with adjustment for NO_2 and PM_{10}, respectively. The results using adults and elderly, and males and females TB outpatient data were compared. The points indicate central estimates and vertical lines indicate 95% confidence intervals. In the analysis, daily average SO_2 with 1% extreme concentrations were excluded.

Figure S2. Exposure-response curves for daily average SO_2 at lag_3 and lag_{03} days and risks for the onset of TB symptoms in single-pollutant and two-pollutant models with adjustment for NO_2 or PM_{10}. A natural spline smoother with 4 df was applied on the SO_2 concentration. The solid line represents central estimates and the envelopes represent 95% confidence intervals. In the analysis, daily average SO_2 with 1% extreme concentrations were excluded.

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Ethical Approval

The study has been reviewed and received approval by the Joint Chinese University of Hong Kong and New Territories East Cluster Clinical Research Ethics Committee (Ref. NO. CRE 044-013).

Competing financial interests declaration:

All authors declare they have no actual or potential competing financial interest.

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