Title:

Acute exposure to sulfur dioxide and mortality: Historical data from Yokkaichi, Japan

Running title:

Sulfur dioxide and mortality in Yokkaichi

Authors:

Takashi Yorifuji *Correspondence

Department of Human Ecology, Graduate School of Environmental and Life Science, Okayama University, Okayama, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan, e-mail: yorichan@md.okayama-u.ac.jp

Saori Kashima

Department of Public Health and Health Policy, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan; E-mail: white-eye@hiroshima-u.ac.jp

Made Ayu Hitapretiwi Suryadhi

Department of Human Ecology, Graduate School of Environmental and Life Science, Okayama University, Okayama, Japan; E-mail: pp3u7x7r@s.okayama-u.ac.jp

Kawuli Abudureyimu

Department of Human Ecology, Graduate School of Environmental and Life Science, Okayama University, Okayama, Japan; E-mail: psyi3opg@s.okayama-u.ac.jp

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Ethics:

The analyses of national data (non-linked, anonymized data) are considered exempt from the need for ethical review according to the Ethical Guidelines for Epidemiological Research in Japan. Ethical approvals were therefore not sought for this study.

Conflicts of interests:

None declared

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Abstract:

We examined the association between acute exposure to sulfur dioxide (SO_2) and mortality, using historical data from 1972–1991 in Yokkaichi, Japan. We used a time-stratified case-crossover study design. We included all causes of death, excluding external causes, between 1972 and 1991 in Yokkaichi and the neighboring town, Kusu of the Mie Prefecture (N=29,839). We obtained daily estimations of SO_2 concentrations during the study period. We then conducted conditional logistic regression analysis to examine association between SO_2 exposure and all-cause and cause-specific mortality. Exposure to SO_2 increased the risk of all-cause and cause-specific mortality in a non-linear manner. The relationship between SO_2 exposure and mortality outcomes remained after adjustment for co-pollutants such as particulate matter and nitrogen dioxide. Historical data from Yokkaichi, Japan, showed that SO_2 exposure increased the risk of all-cause and cause-specific mortality.

Keywords:

Air pollution; Cardiovascular disease; Epidemiology; Sulfur dioxide; Respiratory disease; Yokkaichi Asthma

Abbreviations:

CI: confidence interval; COPD: chronic obstructive pulmonary disease; ICD: International

Classification of Diseases; IQR: interquartile range; NO_2: nitrogen dioxide; OR: odds ratio; PAPA: Public Health and Air Pollution in Asia; PM: particulate matter; ppb: parts per billion; SO_2: sulfur dioxide; SPM: suspended particulate matter

Contents:

135 words for abstract, 2481 words for main text, 24 references, 4 tables, 3 figures, and 1 online table

Introduction

In the mid-20th century, severe air pollution events, for example, in the Meuse Valley in 1930,[1] and in London in 1952,[2] suggested that severe air pollution is associated with adverse health outcomes. Japan also experienced a severe air pollution event in Yokkaichi city in the 1960s and 1970s. [3] The incident is commonly known as Yokkaichi asthma, which is one of the four major pollution-related diseases in Japan, along with Minamata disease (methylmercury poisoning), Niigata Minamata disease (the same), and Itai-Itai disease (cadmium poisoning). The pollutant responsible for Yokkaichi asthma was sulfur dioxide (SO_2), produced by a large petrochemical complex that used crude oil with high sulfur content from the Persian Gulf. Fortunately, subsequent emission controls reduced the concentration of SO_2 in the area. Although previous ecological studies demonstrated associations between exposure to SO_2 and adverse respiratory health outcomes, such as bronchial asthma and chronic bronchitis,[4,5] epidemiological evidence from this historical incident are limited.

Numerous epidemiological studies have demonstrated associations between SO_2 exposure and negative health outcomes,[6-8] but there is uncertainty as to the causal relationship between SO_2 and adverse health outcomes. Some argue that SO_2 may work as a surrogate for the true source of pollution,[9,10] i.e., the association observed between SO_2 exposure and health outcomes may be confounded by other co-pollutants. However, several air pollution studies based in Asian countries demonstrated associations between SO_2 exposure and negative health outcomes even after adjustment of co-pollutants such as particulate matter (PM) and nitrogen dioxide (NO_2).[11,12]

In this study, therefore, we aimed to examine the association between acute exposure to SO_2 and mortality using historical data from 1972–1991 in Yokkaichi city, Japan. As SO_2 exposure was mainly responsible for the air pollution incident in Yokkaichi

and subsequent emission controls for the factory reduced the concentration dramatically, such a wide range of exposure may provide some insights regarding the effect(s) of SO_2 exposure as well as the concentration-response relationship between SO_2 exposure and health outcomes.

Methods

Study area and participants

After Yokkaichi was devastated during the second world war, the spinning and ceramic engineering were the city's main industries. In 1957, a large petrochemical complex was constructed in the eastern part of the city, along the coastline (Figure 1).[3] The city was soon known as the 'City of Petroleum', and produced nearly a quarter of the petrochemical products in Japan at the time.[5] The crude oil used in the complex had a high sulfur content (more than 3%), which induced SO_2 pollution. SO_2 emissions from the complex exceeded 100,000 tons per year.[4] As the complex was located close to the local community, residents living in the vicinity of the complex began to experience respiratory symptoms after the operation. As a result of successful lawsuits by local residents, area-wide controls on total SO_2 emissions were implemented in 1972, which led to a gradual reduction in the concentration of SO_2 in the area (Figure 2). The current annual SO_2 concentration in the Yokkaichi city is below 2 parts per billion (ppb).[13]

We targeted people living in Yokkaichi and a neighboring town, Kusu, of the Mie Prefecture, Japan, who died from any cause, excluding external causes, between January 1972 and December 1991 (N=29,839). Kusu is now a part of Yokkaichi city as a result of a municipal merger in 2005; unless otherwise specified, all subsequent references in this article to 'Yokkaichi' include Kusu. We began data collection in 1972 as mortality data were available in digital format from that year onwards. The study areas are located in the

middle of the country and both areas were severely affected by the SO_2 emitted by the petrochemical complex (Figure 1). The total size of the both areas was 202.9 km^2; the total population in 1975 was 258,887.

Study design

We used a time-stratified case-crossover study design[14] and divided the study period into strata of one month each. We selected control (or reference) periods from all days falling on the same days of the week in the same stratum as the case periods (i.e., mortality).

Air pollution data

From the Mie Prefectural government, we obtained hourly concentrations of SO_2 measured at four monitoring stations in Yokkaichi during the study period (Figure 1). We calculated daily concentrations only for days with hourly concentrations ≥20 hours.[15] We then calculated a city-wide daily mean SO_2 concentration using the daily concentrations at each monitoring station. When daily concentrations at several monitoring stations were not available, we calculated the city-wide daily mean SO_2 concentration using daily concentrations from other stations where data were available. Despite these imputations, we lacked five daily concentrations (0.07% of eligible days), which occurred sporadically during the study period. For days with missing data, we used the mean of the concentrations recorded on the days immediately before and after the day in question to estimate the missing values.

Mortality

From the Japanese Ministry of Health, Labour, and Welfare, we obtained

electronic data on all deaths in Yokkaichi during the study period (1972–1991). The data were stripped of identifiers. Underlying causes of death were coded per the International Classification of Diseases, revision 8 (ICD-8) for death occurring from 1972–1978 and revision 9 (ICD-9) from 1979–1991. Causes of death of interest were all causes of death, excluding external causes, (ICD-8 000–796; ICD-9 000–799); cardiovascular (390–458; 390–459), including ischemic heart disease (410–414; 410–414) and cerebrovascular disease (430–438; 430–438); and respiratory (460–519; 460–519), including pneumonia (480–486; 480–486) and chronic obstructive pulmonary disease (COPD) and asthma (490–493; 490‑496).

Statistical analyses

After descriptive analysis, we conducted conditional logistic regression analysis to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between SO_2 exposure (lag 0: on the same-day; lag 1: one day earlier; lag 2: two days earlier; lag 01: average of the same-day and one day earlier; and lag 02: average of the same-day and one and two days earlier) and each health outcome. In all analyses, we adjusted for same-day average temperature, same-day relative humidity, and national holiday. From the Japan Meteorological Agency, we obtained daily average temperatures and relative humidity in Yokkaichi for the study period. We used restricted cubic splines with five knots for temperature and three knots for humidity.[16]

We first entered the exposure as a linear term and estimated ORs for an interquartile range (IQR) increase in SO_2 during the study period. We estimated ORs for the entire 20-year study period (1972–1991) and for the 10-year study period separated into two (1972–1981 and 1982–1991). We next entered the exposure as a quartile categorization and estimated ORs for the entire study period, using the lowest quartile as reference.

To evaluate the concentration-response relationship between SO_2 exposure and mortality, we modeled the SO_2 exposure from lag 0 to lag 02 using restricted cubic splines with three knots. After conducting conditional logistic regression analysis with adjustment of the same variables, we predicted ORs and their 95% CIs for all-cause mortality across the range of the observed SO_2 exposure. We used the Stata function xblc to generate predictions.

In sensitivity analysis, to examine the potential confounding by other pollutants, we additionally adjusted for same-day PM exposure (measured as suspended particulate matter [SPM]), or same-day NO_2 exposure. SPM accounts for particulate matter with an aerodynamic diameter less than 7 μm (PM_7). We calculated the daily mean of both pollutants measured at one monitoring station in Yokkaichi (Figure 1). SPM was measured from April 1984, while NO_2 was measured from April 1973. All pollutants were entered into the model as linear terms. Moreover, we changed the knots for restricted cubic splines to evaluate the shape of the concentration-response relationship between SO_2 exposure and mortality.

Stata version 14.2 (Stata Corp. LP, College Station, TX, USA) was used for all analyses.

Results

The mean age of the participants was 70 years and half of them were women (Table 1). Mortality related to cerebrovascular disease was the most common followed by ischemic heart disease and pneumonia. Median SO_2 exposure during the study period was 9.0 ppb. As shown in Figure 2, the SO_2 concentration declined dramatically during the study period; the mean concentration (standard deviation) in 1972 was 32.9 (11.4) ppb, compared with 7.8 (2.7) ppb in 1991. The variabilities of the concentrations separated by days of the week also declined from 1971 to 1991 (Online Table 1).

For the first half and for the entire study period, the relationships between SO_2 exposure (as a linear term) and each health outcome were equivocal, except for ischemic heart disease at lag 2 (i.e., SO_2 exposure at 2 days before the event; Table 2). By contrast, in the second half of the study period, SO_2 exposure increased the risk of all-cause (all lags) and cause-specific mortality (cardiovascular disease [lags 2 and 02], cerebrovascular disease [lag 1], pneumonia [lag 2], and COPD and asthma [lag 0]). For example, the OR for all-cause mortality was 1.065 (95%CI: 1.014, 1.118) per 6.9 ppb increase in the same-day exposure to SO_2.

When we used the quartile SO_2 categorization (Table 3), an increase in SO_2 exposure was associated with increased risk of all-cause (lags 1, 2, 01, and 02) and cause-specific mortality (cardiovascular disease [lag 02], cerebrovascular disease [lag 1], pneumonia [lag 2], and COPD and asthma [lag 0]).

The predicted concentration-response relationships are shown in Figure 3. Because few of the SO_2 observations were above 20 ppb, the predictions were less precise above 20 ppb of SO_2 exposure. The risks increased up to 20 ppb of SO_2 exposure, but levelled out or began to decline above that concentration.

The correlation coefficients of SO_2 with SPM and NO_2 in the second half of the study period (1982–1991) were 0.69 and 0.61, respectively. Even when we adjusted for SPM or NO_2 in the sensitivity analysis, the associations between SO_2 exposure and mortality did not change substantially (Table 4). We only show the results from the second half of the study period. In addition, when we changed the knots for restricted cubic splines from three to four or five, the predictions of the concentration-response relationship between SO_2 exposure and mortality did not change substantially (data not shown).

Discussion

We examined the association between acute exposure to SO_2 and mortality by using data from 1972–1991 from Yokkaichi, Japan. We found that SO_2 exposure increased the risk of all-cause and cause-specific mortality in a non-linear fashion. A more linear association between SO_2 and mortality was apparent in the second half of the study period, when SO_2 concentrations declined. The observed associations remained even when levels of co-pollutants were adjusted for.

A previous ecological study in the Yokkaichi area showed a positive correlation between geographical differences in SO_2 level and the incidence of asthmatic bronchitis and upper respiratory infections.[3,5] The correlation coefficients of SO_2 were higher than those of dust fall, which are large particles produced mainly from coal combustion.[17] Another study showed a higher prevalence of chronic bronchitis and obstructive pulmonary disease in SO_2 polluted areas compared to non-polluted areas within Yokkaichi.[3,5] Our study found increased risk for pneumonia as well as COPD and asthma, which is in line with previous data from Yokkaichi. The adverse effects of SO_2 on respiratory health are also supported by the accumulated epidemiological evidence.[6,18] In addition, our study found that the risk of cardiovascular diseases, such as ischemic heart disease and cerebrovascular disease, was also increased, which is also consistent with the accumulated epidemiological evidence.[19-21]

In our study, the risk of all-cause and cause-specific mortality increased, in a non-linear manner, with SO_2 exposure. Our predictions of the concentration-response relationship showed the risks increased up to 20 ppb of SO_2 exposure, but above that concentration the slopes levelled out or began to decline. This is close to the relationships observed in studies conducted in Hong Kong[12] and European countries.[22,23] The European studies, however, cast doubt on the causal relationship: one study from Spain observed that the effects of SO_2 disappeared after adjustment for black smoke[23]; and a study from The

Netherlands suggested that the observed increase in relative risk associated with declining concentrations of SO_2 is counterintuitive.[22] Both studies, therefore, argue that SO_2 may work as a surrogate for another pollutant. However, the Hong Kong study mentioned above, [20] the Public Health and Air Pollution in Asia (PAPA) study,[11] and our study all showed robust effect estimates for SO_2 after adjustment for co-pollutants. SO_2 may be more influential in this locality compared with western countries. The non-linear relationship between SO_2 and mortality in our study may be explained by exposure misclassification in the early study period. The petrochemical complex was located in the eastern part of the city, which created a wide range of SO_2 exposures even within the city.[4] This exposure misclassification, possibly non-differential, would have moved the effect estimates toward the null when the concentration of SO_2 was high, especially in the first half of the study period.

SO_2 may directly or indirectly increase the risk of mortality; it is known to cause bronchoconstriction among sensitive groups,[10] and oxidation of SO_2 can form sulfuric acid, which reacts with atmospheric particles or surfaces to form sulfate particles.[24] Indeed, when the SO_2 pollution was severe in Yokkaichi, the concentration of dust fall was relatively low, but Yokkaichi had the lowest pH values for dust fall in the country.[5]

A strength of our study is that we were able to obtain historical data on daily mortality and daily SO_2, SPM, and NO_2 levels. This study also had several limitations. First, we could not obtain the data from the 1960s, when SO_2 pollution was more severe. Second, we could not avoid exposure misclassification because mortality information was available at a city level. Exposure misclassification would have moved the effect estimates toward the null, especially in the first half of the study period. Third, despite our adjustments for co-pollutants, such as SPM and NO_2, there may have been some residual confounding. The presence of smaller particles, such as fine or ultrafine particles, may also have acted as a

confounder. Indeed, although fine particles were not measured during the study period, a daily correlation coefficient between fine particles (i.e., PM less than 2.5 μm in diameter) and SO_2 at one monitoring station, where we obtained concentrations of SPM and NO_2 for the present study, was 0.53 in 2015.

In conclusion, the historical data from Yokkaichi, Japan, showed that SO_2 exposure increased the risk of all-cause and cause-specific mortality. The shape of the concentration-response relationship seems non-linear, which may be explained by exposure misclassification in the early period. Although SO_2 concentration greatly reduced in the study area, SO_2 exposure increased the risk even below the Japanese air quality guideline for SO_2 (i.e., 40 ppb in daily average). Given the possible adverse effect of SO_2, SO_2 exposure would still be a problem in Japan as well as countries facing high concentrations of SO_2.

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Figure legends

Figure 1. Map of the study area.

Figure 2. Trends in sulfur dioxide concentrations in Yokkaichi from 1972–1991.

Figure 3. Predicted shape of the concentration-response relationship between sulfur dioxide exposure and all-cause mortality. The adjusted odds ratios and their 95% confidence intervals for all-cause mortality across the range of the observed sulfur dioxide exposure are shown for: (a) same-day exposure (lag 0); (b) one-day-earlier exposure (lag 1); (c) two-days-earlier exposure (lag 2); (d) average of the same-day and one day earlier (lag 01); (e) and average of the same-day and one and two days earlier (lag 02).