Exposure to Fine Particulate Matter and Acute Upper- and Lower- Respiratory Tract Infections

微粒子状物質への曝露による急性上気道および下気道感染症

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CONTENTS

Acknowledgement
Summary
List of Tables
List of Figure
Chapter 1 Introduction 1
1.1 General Introduction 1
1.2. Study Objectives 2
1.3. Outline 2
Chapter 2 Acute exposure to sulfur dioxide and mortality: Historical data from Yokkaichi, Japan 5
2.1 Introduction 5
2.2 Methods 6
2.2.1 Study area and participants 6
2.2.2 Study design 7
2.2.3 Air pollution data 7
2.2.4 Mortality 8
2.2.5 Statistical analyses 8
2.3 Results 10
2.4 Discussion 11
Chapter 3 Effects of household air pollution from solid fuel use and environmental tobacco smoke on child health outcomes in Indonesia 15
3.1. Introduction 15
3.2. Methods 15
3.2.1. Study Population 15
3.2.2. Indoor Air Pollution Exposure 16
3.2.2.1. HAP: Indoor Air Pollution from Solid-fuel Use 16
3.2.2.2. ETS: Indoor Air Pollution from Smoking 16
3.2.3. Health outcomes 17
3.2.4. Statistical Analysis 17
3.3. Results 18
3.4. Discussion 19
3.5. Conclusion 23
Chapter 4 Exposure to fine particulate matter and acute upper- and lower- respiratory tract infections in children under five years of age in India. 24
4.1. Introduction 24

4.2. Method 25
4.2.1 Source of data 25
4.2.2 Exposure 25
4.2.3 Respiratory tract infection indicators 26
4.2.4 Statistical Analysis 26
4.3. Results 27
4.4. Discussion 28
4.5. Conclusions 30
Chapter 5 General Conclusion 32
TABLES 33
FIGURES 46

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SUMMARY

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.

Then, we assessed the combined effect of household air pollution from solid fuel use and from environmental tobacco smoke and child health outcomes in Indonesia. Methods: Survey subjects self-reported solid fuel use, frequency of indoor smoking, and health outcomes in children. We then evaluated the effect of a combined exposure using multivariate logistic regression. Results: Children exposed to high levels of pollution from solid fuel use had an increased risk of low birth weight, neonatal death, infant death, and acute lower respiratory infection. Exposure to environmental tobacco smoke

increased the risk of acute lower respiratory infection. The combined effect of both pollution sources outweighed the independent risk of each exposure alone. Conclusions: Solid fuel use and environmental tobacco smoke independently increased the risk and child health outcomes and the combined exposure showed the additive effect.

Recently emerging evidence suggests an association between particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) exposure and diabetes risk. However, evidence from Asia is limited. Here, we evaluated the association between $PM_{2.5}$ exposure and the prevalence of diabetes mellitus in one of the most populated countries in Asia, Indonesia. Methods: We used the 2013 Indonesia Basic Health Research, which surveyed households in 487 regencies/ municipalities in all 33 provinces in Indonesia (n = 647,947). We assigned individual exposure to $PM_{2.5}$ using QGIS software. Multilevel logistic regression with a random intercept based on village and cubic spline analysis were used to assess the association between $PM_{2.5}$ exposure and the prevalence of diabetes mellitus. We also assessed the lower exposure at which $PM_{2.5}$ has potential adverse effects. Results: We included 647,947 subjects with a mean age of 41.9 years in our study. Exposure to $PM_{2.5}$ levels was associated with a 10-unit increase in $PM_{2.5}$ (fully adjusted odds ratio: 1.09; 95% confidence interval: 1.05–1.14). The findings were consistent for quartile increases in $PM_{2.5}$ levels and the cubic spline function. Even when we restricted to those exposed to $PM_{2.5}$ concentrations of less than 10.0 $\mu g/m^3$ in accordance with the recommended guidelines for annual exposure to $PM_{2.5}$ made by the World Health Organization, the association remained elevated, especially among subjects living in the urban areas. Hence, we were unable to establish a safe threshold for $PM_{2.5}$ and the risk of

diabetes. Conclusions: Our findings suggest a positive association between $PM_{2.5}$ exposure and prevalence of diabetes mellitus, which is possibly below the current recommended guidelines. Further studies are needed to ascertain the causal association of this finding.

Severe methylmercury poisoning occurred in Minamata and neighboring communities in Japan during the 1950s and 1960s, causing what is known as Minamata disease. Although an increase in stillbirths and a reduced male proportion at birth (i.e., reduced sex ratio) have been reported, no studies have evaluated the impact of exposure on an entire set of infant and birth outcomes. We therefore evaluated the temporal trends of these outcomes in the Minamata area from 1950 to 1974. We focused on the spontaneous/artificial stillbirth rate, crude fertility rate, male proportion at birth, male proportion among stillbirths, and infant mortality. We obtained the number of stillbirths, live births, and infant deaths in Minamata City and Kumamoto Prefecture (as a reference) from 1950 to 1974. After plotting annual figures for each outcome, we divided the study period into five intervals and compared them between Minamata City and Kumamoto Prefecture using the chi-squared test. We observed a slightly increased spontaneous stillbirth rate and decreased artificial stillbirth rate in Minamata City, followed by a reduced crude fertility rate. The crude fertility rates in Minamata City during the period 1955-1965 were significantly lower compared with those in Kumamoto Prefecture ($p < 0.001$). An increase in the male proportion among stillbirths was observed, corresponding to a reduction in the proportion of males at birth in the late 1950s. The impact on infant mortality was equivocal. These descriptive analyses demonstrate a severe regional impact

of methylmercury exposure on a series of birth outcomes in the Minamata area.

As one of the world's polluted regions, we assessed the association between ambient $PM_{2.5}$ levels and acute lower and upper respiratory infection in India. We assessed 55,118 children from the 2015-2016 Demographic Health Survey in India using the information on levels of $PM_{2.5}$ in 2015 and 2016 from the Atmospheric Composition Analysis Group. We used the generalized estimating equation for the analysis reported as odds ratios and 95% confidence intervals for every 10 $\mu g/m^3$ increase and quartiles in $PM_{2.5}$. Every 10 $\mu g/m^3$ increase in levels of $PM_{2.5}$ associated with acute upper respiratory infection (OR 1.02, 95%CI: 1.02-1.03) and acute lower respiratory infection (OR 1.05, 95%CI: 1.03-1.06). This association was confirmed by quartile exposure assessments. Mitigation efforts must be continued implementing higher restrictions in India to ensure safe levels of air.

LIST OF FIGURES

Figure 1. Map of the study area. …….……38

Figure 2. Trends in sulfur dioxide concentrations in Yokkaichi from 1972–1991……39

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)….…….....40

Figure 4. The distribution of particulate matter ($PM_{2.5}$) levels in 2015-2016 in India…..41

Figure 5. Restricted cubic spline of the association between exposure to particulate matter ($PM_{2.5}$) and the prevalence of AURI adjusted for child's age, child's sex, mother's education, mothers smoking status, and population density……....42

Figure 6. Restricted cubic spline of the association between exposure to particulate matter ($PM_{2.5}$) and the prevalence of ALRI adjusted for child's age, child's sex, mother's education, mothers smoking status, and population density…….43

LIST OF TABLES

Table 1. Characteristics of people who died from all causes, excluding external causes, in Yokkaichi, Japan, 1972–1991…….…….26

Table 2. Adjusted odds ratios per interquartile range increase in SO_2 concentration from 1972–1991, Yokkaichi, Japan. ……...…….27

Table 3. Adjusted odds ratios for mortality outcomes at different levels of SO_2, compared with first quartile as reference. …….28

Table 4. Adjusted odds ratios per interquartile range increase in SO_2 during the second half of the study period (1982–1991) obtained from a two-pollutant model including SO_2 and suspended particulate matter or nitrogen dioxide. …….….29

Table 5. Demographic characteristics of children included in the study (N = 36,842) ... 30

Table 6. Incidence and odds ratios (ORs) of household air pollution from solid fuel use and child health outcomes in Indonesia (N = 36,726) …….……...……31

Table 7. Incidence and odds ratios (ORs) of environmental tobacco smoke exposure and child health outcomes in Indonesia (N = 36,805) …….....……...32

Table 8. Incidence and adjusted odds ratios (ORs) for the combined effect of household

air pollution from solid fuel use (HAP) and environmental tobacco smoke (ETS) and child health outcomes in Indonesia (N=36,709) ...…….33

Table 9. Sociodemographic characteristics of subjects in India (N=55,118) ….……34

Table 10. Odds ratios and 95% confidence intervals for the association between exposure to particulate matter ($PM_{2.5}$) levels and AURI and ALRI in India during 2015-2016.…….……35

Table 11. Effect modification of the association between AURI and ALRI and exposure to particulate matter ($PM_{2.5}$) levels in India during 2015-2016……36

LIST OF SUPPLEMENTARY TABLES

Supplementary 1. Odds ratios and 95% confidence intervals for the association between exposure to particulate matter ($PM_{2.5}$) levels and AURI and ALRI in India during 2015-2016 adjusted using wealth index instead of mother's education…….…….37

Supplementary 2. Odds ratios and 95% confidence intervals for the association between exposure to particulate matter ($PM_{2.5}$) levels and AURI and ALRI in India during 2015-2016 (Rural and Urban subjects)……..…….....38

Chapter 1 Introduction

1.1 General Introduction

Short-term exposure to air pollution can cause and aggravate a number of respiratory conditions, including asthma, bronchitis and chronic obstructive pulmonary disease (COPD). This association between air pollution exposure and the risks to human health has been a public health concern for over 700 years.

Sources of air pollution include natural (e.g. volcano eruption, forest fire, dust storms, etc.) and anthropogenic sources (e.g. industrial sources, open dumps, automobiles, home furnaces, home fire places and stoves, backyard barbeque grills, and open burning of refuse and leaves) (Vallero, 2008). Types of pollutants include particulate matter (PM), black carbon, ground-level ozone, NO_2, SO_2, and carbon monoxide (CO).

In the mid-20th century, severe air pollution events, for example, in the Meuse Valley in 1930, and in London in 1952, 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. The incident is commonly known as Yokkaichi asthma, which is one of the four major pollutions 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, epidemiological evidence from this historical incident are limited.

1.2. Study Objectives

In general, we aim at assessing associations between exposure to air pollution and health outcomes in children, specifically:

1. To evaluate the association between air pollution (NO_2 and SO_2) and health outcomes in children aged 0–3 years in Indonesia.
2. To evaluate the association between air pollution and health in Japan.
3. To evaluate the effect of combined exposure ($PM_{2.5}$, PM_{10}) on child birth and child health outcomes in India.

1.3. Outline

In Chapter 1 We examined the association between acute exposure to sulfur dioxide (SO_2) and mortality, using historical data from 1972–1991 in Yokkaichi, Japan.

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.

In Chapter 2 We presented our findings on the combined effect of household air pollution from solid-fuel use and from environmental tobacco smoke on child health outcomes in Indonesia. Survey subjects reported solid-fuel use, frequency of indoor smoking, and health outcomes in children. We then evaluated the effect of a combined

exposure using multivariate logistic regression. Children exposed to high levels of pollution from solid-fuel use was associated with an increased risk of low birth weight, neonatal death, infant death, and acute lower respiratory infection. Exposure to environmental tobacco smoke associated with an increase in the risk of acute lower respiratory infection. The combined effect of both pollution sources increased the risk of adverse child health outcomes. Solid-fuel use and environmental tobacco smoke independently associated with an increased risk of child health outcomes, but combined exposure outweighed the independent risk of each exposure alone.

In Chapter 3 Recently emerging evidence suggests an association between particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) exposure and diabetes risk. However, evidence from Asia is limited. Here, we evaluated the association between $PM_{2.5}$ exposure and the prevalence of diabetes mellitus in one of the most populated countries in Asia, Indonesia.

We included 647,947 subjects with a mean age of 41.9 years in our study. Exposure to PM2.5 levels was associated with a 10-unit increase in $PM_{2.5}$ (fully adjusted odds ratio: 1.09; 95% confidence interval: 1.05–1.14). The findings were consistent for quartile increases in $PM_{2.5}$ levels and the cubic spline function. Even when we restricted to those exposed to $PM_{2.5}$ concentrations of less than 10.0 $\mu g/m^3$ in accordance with the recommended guidelines for annual exposure to $PM_{2.5}$ made by the World Health Organization, the association remained elevated, especially among subjects living in the urban areas. Hence, we were unable to establish a safe threshold for $PM_{2.5}$ and the risk of diabetes.

Finally, in Chapter 4 As one of the world's polluted regions, we assessed the

association between ambient $PM_{2.5}$ levels and acute lower and upper respiratory infection in India. We assessed 55,118 children from the 2015-2016 Demographic Health Survey in India using the information on levels of $PM_{2.5}$ in 2015 and 2016 from the Atmospheric Composition Analysis Group. We used the generalized estimating equation for the analysis reported as odds ratios and 95% confidence intervals for every 10 $\mu g/m^3$ increase and quartiles in $PM_{2.5}$. Every 10 $\mu g/m^3$ increase in levels of $PM_{2.5}$ associated with acute upper respiratory infection (OR 1.02, 95%CI: 1.02-1.03) and acute lower respiratory infection (OR 1.05, 95%CI: 1.03-1.06). This association was confirmed by quartile exposure assessments. Mitigation efforts must be continued implementing higher restrictions in India to ensure safe levels of air.

Chapter 2 Acute exposure to sulfur dioxide and mortality: Historical data from Yokkaichi, Japan

2.1 Introduction

In the mid-20th century, severe air pollution events, for example, in the Meuse Valley in 1930 (Nemery 2001), and in London in 1952, (Logan 1952) 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. (Yoshida et al. 2007) 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, (Imai et al. 1986, Yoshida et al. 1966) epidemiological evidence from this historical incident are limited. Numerous epidemiological studies have demonstrated associations between SO_2 exposure and negative health outcomes (HEI 2010, Stieb et al. 2002, Stieb 2003) but there is uncertainty as to the causal relationship between SO_2 and adverse health outcomes. Some argue that SO2 may work as a surrogate for the true source of pollution (WHO 2013, WHO 2006) 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).(Kan et al. 2010, Wong 2001) 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.

2.2 Methods

2.2.1 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) (Yoshida et al. 2007). The city was soon known as the 'City of Petroleum', and produced nearly a quarter of the petrochemical products in Japan at the time (Yoshida et al. 1966). 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, areawide 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) (Mie Prefectural Government 2017).

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.

2.2.2 Study design

We used a time-stratified case-crossover study design (Janes et al. 2005) 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).

2.2.3 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 (National Institute for Environmental Studies of Japan 2017). 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.

2.2.4 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).

2.2.5 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 (Yorifuji et al.2016).

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 mm (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.

2.3 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 SO2 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., SO2 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 SO2 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.

2.4 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 (Logan 1952, Yoshida et al. 1966). The correlation coefficients of SO_2 were higher than those of dust fall, which are large particles produced mainly from coal combustion (Ministry of the Environment in Japan1969). 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 (Logan 1952, Yoshida et al. 1966). 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 (HEF 2010, Yorifuji et al. 2015). 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 (Cai et al. 2016, Shah et al. 2015).

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 (Wang et al. 2001) and European countries (Buringh et al., 2000, Schwartz 2001). 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 (Schwartz et al., 2001); and a study from The Netherlands suggested that the observed increase in relative risk associated with declining concentrations of SO_2 is counterintuitive. Both studies, therefore, argue that SO_2 may work as a surrogate for another pollutant. However, the Hong Kong study mentioned above, the Public Health and Air Pollution in Asia (PAPA) study, 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. 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 (WHO 2006), and oxidation of SO_2 can form sulfuric acid, which reacts with atmospheric particles or surfaces to form sulfate particles(Landis WG et al., 2011). 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 (Yoshida 1966). 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 1960 s, 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 mm 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 nonlinear, 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.

Chapter 3 Effects of household air pollution from solid fuel use and environmental tobacco smoke on child health outcomes in Indonesia

3.1. Introduction

Indoor air pollution is defined as chemical, biological, and physical contamination of indoor air and generally refers to HAP derived from the use of solid fuels for cooking (Landrigan and Etzel, 2014). The World Health Organization has estimated that HAP contributed to 4.3 million deaths in 2012 (World Health Organization, 2014). Another notable form of indoor air pollution is caused by second-hand smoke, known as passive smoking or ETS. It is estimated that around 0.9 million deaths occurred in 2016 because of ETS, and 56,340 of these casualties were children under the age of 10 years (GBD 2016 Risk Factors, 2017).

Previous studies have shown that exposure to HAP and ETS is independently associated with adverse child health outcomes such as stillbirth, LBW, neonatal and infant death, and acute respiratory infections (Amegah et al., 2014, Dherani et al., 2008, Epstein et al., 2013, Jackson et al., 2013, Leonardi-Bee et al., 2011, Po et al., 2011, Pope et al., 2010, Rinne et al., 2007, Salmasi et al., 2010, Smith et al., 2000, Tielsch et al., 2009, Ward et al., 2007, Zhang and Smith, 2007). Although young children and pregnant women can be exposed to both sources simultaneously, few studies have examined the impact of joint exposure to HAP and ETS (Akinyemi et al., 2016).

3.2. Methods

3.2.1. Study Population

We identified study subjects from the birth records of the 2012 IDHS, which includes

demographic information, indoor air pollution data, and records of health outcomes. The survey was a cross-sectional study that collected data between May 7 and July 31, 2012 in all 33 provinces in Indonesia. The survey targeted women aged 15–49 years who provided information on all births or stillbirths through 2012 (n = 45,607). In the present study, we focused on singleton births (including stillbirths) between 2002 and 2012 with de-jure residence. We selected 2002 as the lower cut-off to ensure a large sample (36,842 children) for the analyses.

3.2.2. Indoor Air Pollution Exposure

3.2.2.1. HAP: Indoor Air Pollution from Solid-fuel Use

The IDHS queried subjects on HAP with the question "What type of fuel does your household mainly use for cooking?" We then assumed that children were highly exposed when solid fuel (coal, lignite, charcoal, wool, or straw/shrubs/grass) was used for cooking. Conversely, we assumed that children had low levels of exposure to indoor air pollution when clean fuel (electricity, propane/natural gas, biogas, or kerosene) was used for cooking. We excluded the records of 92 (0.3%) children whose mothers replied "no food cooked in the house" or "other", as well as 24 (0.07%) children whose records lacked information on cooking.

3.2.2.2. ETS: Indoor Air Pollution from Smoking

The IDHS queried subjects on ETS with the question "How often does anyone smoke inside your house? Would you say daily, weekly, monthly, less than monthly, or never?" We assumed that children were highly exposed to indoor smoking when the smoking frequency inside the house was daily, and that children had low levels of

exposure to indoor smoking when the smoking frequency was lower.

3.2.3. Health outcomes

The IDHS also included information on the children's health outcomes. We identified health outcomes in the present study from questions related to stillbirth, LBW, neonatal death, infant death, acute upper respiratory infection, and acute lower respiratory infection. LBW was defined as weight at birth below 2500 grams. We defined children whose age at death was 0– 28 days as neonatal deaths and those whose age at death was 0–11 months as infant deaths. AURI was evaluated by asking whether the child had suffered from a cough in the last 2 weeks and whether the cough was accompanied with short, rapid and difficulty breathing for ALRI.

3.2.4. Statistical Analysis

We used logistic regression to evaluate the association between the two types of indoor air pollution and health outcomes and we put both exposures in a separate model. We estimated ORs with 95% CIs using the low-exposure category as a reference. We used GEE analysis to account for correlations between respondents. We first estimated crude ORs and then adjusted for potential confounding factors such as child's age (continuous), child's sex (dichotomous), mother's age (continuous), mother's education level (categorical), and residential area (urban or rural, dichotomous). This information was derived from the IDHS. Maternal education was categorized as no education, primary education, secondary education, and higher education.

In the subsequent analysis to evaluate the impact of joint exposure to indoor air pollution from solid fuel use and smoking, we combined the exposures into four exposure

categories: Low exposure to HAP and ETS; high exposure to HAP and low exposure to ETS; low exposure to HAP and high exposure to ETS; high exposure to HAP and ETS. We then examined the effect of combined exposure on health outcomes using the same generalized estimating equation approach and adjusting for the same potential confounders.

We then performed two sensitivity analyses. First, we adjusted for the household wealth index instead of maternal education as an indicator of socioeconomic status. The wealth index was available from the 2012 IDHS, and was generated using principal component analysis based on the household's assets (e.g., televisions and bicycles), type of housing construction, and access to water and sanitation facilities. Second, we further restricted the subjects to those households that cooked inside the house to reduce exposure misclassification. We used the question "Is the cooking usually done in the house, separate building, or outdoors" from the 2012 Demographic Health Survey questionnaire to select subjects.

We used Stata 13.1 (StataCorp LLC, College Station, Texas, USA) for the analysis. The IDHS received ethical approval from the relevant ethics boards. We did not obtain additional ethical approval as we received anonymized IDHS data.

3.3. Results

The mean age of the children was 4.8 years (Table 5). Approximately 40% were exposed to high levels of indoor air pollution from solid-fuel use, and around 70% were exposed to high levels of indoor air pollution from smoking.

HAP from solid-fuel use was associated with an increased risk of several health outcomes even after adjusting for confounders and for ETS (Table 6). Children exposed

to high levels of HAP from solid-fuel use had an increased risk of LBW, neonatal death, infant death, and acute lower respiratory infection, compared with children exposed to low levels of HAP from solid-fuel use.

Table 7 lists the results from multivariate analysis for ETS and health outcomes. Although some effect estimates were elevated, ETS was only associated with increased risk of acute lower respiratory infection.

When we combined both exposures, 20.1% of children were exposed to neither HAP from solid-fuel use nor ETS, 9.8% were exposed to high pollution levels from solid-fuel use, 38.3% were exposed to high pollution levels from ETS, and 31.8% were exposed to pollution from both solid-fuel use and ETS (Table 8). While exposure to HAP from solid-fuel use or to 18 ETS independently increased the risk of several health outcomes, the combined exposure yielded higher ORs in some outcomes. For example, the ORs for acute lower respiratory infection were 1.21 (95% CI: 0.98–1.50) for HAP from solid-fuel use and 1.12 (95% CI: 0.97– 1.29) for exposure to ETS, but 1.36 (95% CI: 1.16–1.61) for exposure to both.

After adjusting for the wealth index instead of maternal education in the sensitivity analysis, the values did not change substantially (Supplementary Table 3). Also, no significant changes to the values were found after restricting the subjects to those households that cooked inside the house (Supplemental Table 4).

3.4. Discussion

In the present study, we evaluated the effect of combined exposure to indoor air pollution from solid-fuel use and ETS on birth and child health outcomes in Indonesia. We observed an increased risk of LBW, neonatal death, infant death, and acute lower respiratory infection. Moreover, a combined exposure to HAP from solid-fuel use and

ETS was more detrimental than exposure to each pollution source alone.

The observed adverse effects of HAP from solid-fuel use on LBW, neonatal mortality, infant mortality, and acute lower respiratory infection are consistent with those of previous studies (Ezeh et al., 2014, Khan et al., 2017). Khan and colleagues showed that HAP significantly increased the risk of LBW and acute respiratory infection in children in Bangladesh (Khan et al., 2017). The association between exposure to solid-fuel pollution and infant mortality is well-established, and Neogi and colleagues found an adverse effect on 19 neonatal mortality in India as well (Ezeh et al., 2014, Kashima et al., 2010, Neogi et al., 2015). Another study in India reported that exposure to solid-fuel pollution increased the risk of child deaths at 1–4 years; these reports support our findings (Bassani et al., 2010).

We also found that ETS exposure associated with an increased risk of acute lower respiratory infection and several health outcomes, although some of the effect estimates did not reach statistical significance. Our findings on acute lower respiratory infection supports the findings of other studies suggesting an association between ETS and acute lower respiratory infection (Cheraghi and Salvi, 2009, Jones et al., 2011). Compared with the effects of HAP from solid-fuel use, the adverse effect of ETS was not as apparent, which may be explained in part by lower exposure variation owing to the high prevalence of indoor smoking inside in the study population; approximately 70% of the households surveyed had daily smokers.

More than 30% of children were exposed to pollution from both solid-fuel use and ETS, underscoring the vulnerability of children to multiple health risks in developing countries. Moreover, the combined exposure was more harmful than each exposure alone. Because previous studies controlled for smoking in analyses of the effects of indoor air

pollution, we cannot compare our findings with theirs. We found only one study that investigated the association between the combined effects of maternal smoking and solid-fuel use on infant and child mortality; the authors reported findings similar to ours, concluding that a combined exposure to both solid-fuel pollution and cigarette smoke was more harmful than exposure to each pollutant alone (Akinyemi et al., 2016). Our findings concur with those of the Lancet Commission on Pollution and Health, which estimated that the health burden from multiple 20 exposures would be greater than the simple arithmetic sum of estimated deaths from a single exposure. Future studies should assess the combined effects of several sources of pollution, as evaluating exposure to a single source of pollution may underestimate the true effects (Landrigan et al., 2017).

The adverse effects of HAP from solid-fuel use and ETS on child health outcomes are plausible. Small particulates and carbon monoxide are the two main air pollutants attributable to these exposures. Particulate matter with a diameter less than 10 μm exerts significant adverse health effects as it reaches the lower segments of the lungs and even enters the bloodstream (EPA, 2016). Moreover, particulate matter exposure during pregnancy can cause oxidative stress, inflammation, and coagulation and impair endothelial function and hemodynamic responses (Kannan et al., 2006). High concentrations of carbon monoxide dysregulate carboxyhemoglobin binding and can lead to death (EPA, 2017). Women exposed to carbon monoxide during pregnancy can develop increased carboxyhemoglobin binding, disrupting the supply of oxygen to the developing fetus (Di Cera et al., 1989, EPA, 2010). Restriction of oxygen that leads to hypoxia can be critical, especially in the second and third trimesters, when oxygen is required for normal fetal organogenesis and growth (Hutter et al., 2010). Prenatal exposure may also lead to adverse postnatal effects that result in neonatal and infant death. Levels of

particulate matter and carbon monoxide from biomass burning in homes with inefficient ventilation, mostly in developing countries, have been shown to exceed the World Health Organization Air Quality Standards (Bartington et al., 2017). Although we cannot conclude definitively that a combined exposure to HAP from solid-fuel use and ETS is more 21 harmful than the effects of exposure to only one source of pollution, the underlying mechanisms may act in synergy to exert greater adverse effects.

There are several strengths to our study. First, few studies have examined the effects of a combined exposure to multiple sources of indoor air pollution. Second, we used a large sample and included data from all 33 provinces in Indonesia. Third, the response rate to the survey was high (99%). Fourth, the questionnaires used in the survey were validated prior to the study.

There are also some limitations. First, information was self-reported, which may lead to misclassification of the exposure or outcome status, although the misclassification would be nondifferential, moving the effect estimates toward the null (Rothman, 2012). Second, we do not have any information on ventilation from the 2012 IDHS, which would define the level of exposure among the subjects. But, a study in Indonesia demonstrated that concentrations of the pollutants were still high although the houses had ventilation (Huboyo et al., 2014). Moreover, restricting the subjects to those households that cooked inside the house to minimize exposure misclassification resulted in no substantial changes to the main result. Third, because of the design of the survey, the 2012 IDHS did not measure any air quality data derived from HAP and ETS. However, previous epidemiological studies have used the same method of exposure assignment (Akinyemi et al., 2016, Bassani et al., 2010, Ezeh et al., 2014, Kashima et al., 2010, Khan et al., 2017) with ours and some experimental studies demonstrated that HAP and ETS actually

increased the concentrations of pollutants such as particulate matter and carbon monoxide indoors (Bartington et al., 2017, Goniewicz et al., 2009, Semple et al., 2015). Indeed, 22 the study from Indonesia mentioned above demonstrated that mean concentrations of small particles (i.e., particulate matter with a diameter less than 2.5 μm) in households with indoor cooking exceeded 700 μg/m3 (22 to 23 hours) and were much higher than the WHO guideline value (i.e. 25 μg/m3 for 24 hours) although these households had ventilation (World Health Organization, 2014). However, to confirm findings of this study, future studies assessing concentrations of air pollutants for HAP from solid-fuel use and ETS are needed. Fourth, residual confounding from household socioeconomic status or parental medical history is possible; however, adjusting for maternal education or familial wealth index did not result in substantial differences. Moreover, we do not have information on other indoor air pollutants such as insecticide spray and household cleaners or bleaches. Because this information was not available in the 2012 IDHS dataset, future studies will benefit from adjusting for these factors.

3.5. Conclusion

HAP from solid-fuel use and ETS independently associated with an increased risk of adverse child health outcomes in Indonesia and a combined exposure outweighed the independent risk of each source of pollution, showing the presence of additive effect. However, future studies evaluating concentrations of pollutants for HAP from solid-fuel use and ETS are required to confirm findings of this study. Because children are vulnerable to multiple risks in developing countries, community education and environmental policies regulating indoor air pollution from sources such as solid-fuel use and ETS are essential for mitigating the associated adverse health effects.

Chapter 4 Exposure to fine particulate matter and acute upper- and lower- respiratory tract infections in children under five years of age in India.

4.1. Introduction

Deaths associated with $PM_{2.5}$ exposure reached 4.2 million in 2015 representing 7.6% of the total global deaths with more than 50% of the deaths occurring in east and south Asia (Cohen et al. 2017). A systematic review performed from January 2004 to November 2014 assessing the association between ambient air pollution and respiratory health of children in Canada, showed a detrimental effect of ambient air pollution on respiratory health of the children, at levels below the Canadian and United States standards (Rodriguez-Villamizar et al. 2015). As one of the world's polluted regions, more than 50% of residents in India are exposed to levels of $PM_{2.5}$ which is higher than the World Health Organization's annual standard (Dey et al. 2012, Pawankar et al. 2020).

The total disability-adjusted life years (DALYs) in India from chronic respiratory disease (COPD) increased from 4.5% to 6.4% in 1990 and 2016, respectively. In 2016, air pollution was responsible for 53.7% (43.1-65) of the DALYs caused by COPD in India (Collaborators IS-LDBIC,2016). While many studies in India mainly focussed on the effect of solid-fuel use and health including young children, not many have assessed $PM_{2.5}$ as the main exposure. However, studies that addressed exposure to PM_{10}, suggest a positive association between PM_{10} exposure and respiratory symptoms in children in India (Mahapatra et al. 2011, Siddique et al. 2020). Here, we attempt our analysis using $PM_{2.5}$ as our main exposure and study its effect on acute upper and lower respiratory

infection in young children in India.

4.2. Method

4.2.1 Source of data

We used the births dataset for India in 2015-2016. This is available from the following website: https://dhsprogram.com/data/available-datasets.cfm. This survey collects information on monitoring and impact evaluation in population, health, and nutrition areas, carried out from 20th January 2015 through 4th December 2016. The survey is also known as the 2015-2016 National Family Health Survey (NFHS-4) for India (International Institute for Population Sciences, 2016). Subjects were identified through a stratified two-stage sampling method, resulting in a total of 628,900 selected households with a response rate that reached 98%. The Standard DHS dataset for India in 2015-2016 constituted 28,526 clusters. However, 419 clusters had missing information of $PM_{2.5}$ in the modeled dataset. As a result, we included 28,107 clusters in the analysis. Geocode information for rural clusters was displaced up to 10 kilometers to protect the subject's information. Hence, we restricted our analysis to those living in urban areas.

4.2.2 Exposure

We used levels of $PM_{2.5}$ for the global annual surface estimates for 2015 and 2016 provided by the Atmospheric Composition Analysis Group at Washington University. The estimates were retrieved using aerosol optical depth (AOD) (NASA MODIS C6.1, MISR v23, MAIAC C6) and SeaWiFS satellite products which were then combined and related with surface levels of $PM_{2.5}$ and AOD and calibrated with geographically weighted

regression (GWR) (Hammer et al. 2020). For the exposure, we used annual mean values of $PM_{2.5}$ at 0.01° x 0.01° (approximately 1 km x 1 km). The dataset is publicly available from the following website: https://sites.wustl.edu/acag/datasets/surface-pm2-5/. We assessed levels of $PM_{2.5}$ in India in 2015 and 2016 based on cluster information in the geographic dataset from the Standard DHS dataset for India in 2015-2016 which provided geocode data, then used the mean level as the main exposure.

4.2.3 Respiratory tract infection indicators

We used acute upper respiratory tract infection (AURI) and acute lower respiratory tract infection (ALRI) as the health outcomes in this study. The survey acquired this information based on symptoms experienced by children under five years of age, two weeks preceding the survey (International Institute for Population Sciences 2016). We identified AURI from the question "Whether the child had suffered from a cough over the past two weeks". Furthermore, ALRI was identified from the question "Whether the child had suffered from rapid breathing when he/she had the cough". This definition has been used as an outcome of interest in many studies (Hollm-Delgado et al. 2010, Kashima et al. 2014, Mosites et al. 2019).

4.2.4 Statistical Analysis

To assess the association between exposure to $PM_{2.5}$ levels and AURI and ALRI, we used the generalized estimating equation (GEE) analysis. We used this analysis to consider correlations within mothers. In the final model, we adjusted for child's age (continuous: years), child's sex (dichotomous: male/female), mother's education

(categorical: no education, primary, secondary, and higher), mother's smoking status (dichotomous: no/yes), solid-fuel use (non-solid fuel and solid-fuel), and population density (continuous). Population density data was available from the geospatial covariates dataset from the Standard DHS dataset for India in 2015-2016 at the cluster level. We assessed the shape of the association between levels of $PM_{2.5}$ and the prevalence of AURI and ALRI with the restricted cubic spline analysis with three knots for $PM_{2.5}$. We tested whether a child's sex and solid fuel modified our findings by performing a stratified analysis. We determined differences in effect estimates by adding an interaction term between the covariates and the exposure using the fully-adjusted model (Suryadhi et al. 2019, Suryadhi et al. 2020). In the sensitivity analysis, we adjusted for the wealth index (categorical: poorest, poorer, middle, richer, and richest) instead of the mother's education as an indicator of socioeconomic status. The calculation for wealth index used principal component analysis of the ownership of consumer goods (i.e. television, bicycle, and car) and conditions of the living space (i.e. drinking water, toilet facilities, and flooring materials) (International Institute for Population Sciences 2016). The results reported odds ratios with 95% confidence intervals for every 10 $\mu g/m^3$ increase in $PM_{2.5}$ and quartiles in $PM_{2.5}$. For the analysis, we used STATA 16.0 (StataCorp, College Station, TX, USA). As we received anonymized dataset, we did not seek additional ethical clearance for this study.

4.3. Results

We included around 55,118 children in our study. The prevalence of AURI reached 11.5%, whereas 5.1% for ALRI (Table 2). The annual mean level of $PM_{2.5}$ ranged from 8,55 $\mu g/m^3$ to 133,70 $\mu g/m^3$ in India from 2015 to 2016.

Every 10 μg/m^3 increase in levels of $PM_{2.5}$ was associated with AURI (OR 1.02, 95%CI: 1.02-1.03) and ALRI (OR 1.05, 95%CI: 1.03-1.06) in children in India during 2015-2016. This association was also found for quartiles of $PM_{2.5.}$ We found that the association between short-term exposure to $PM_{2.5}$ was strongest at the highest quartile (94.15-133.70 μg/m^3) when compared to the lowest quartile (8.55-43.75 μg/m^3) for both AURI (OR 1.13, 95%CI: 1.04-1.23) and ALRI (OR 1.44, 95%CI: 1.28-1.62) (Table 2). However, we observed an inverse association for AURI at the second quartile (Q2).

Results from the restricted cubic spline analysis suggested that the association between short-term exposure to $PM_{2.5}$ and AURI steadily increased with increasing levels of $PM_{2.5}$ (Figure 2), with ALRI shown to slowly lower but remain significant at above 80 μg/m^3 (Figure 3). Furthermore, we found that child's sex or solid fuel use did not modify the results (Table 3). When we used the wealth index instead of the mother's education in the analysis, we found no meaningful changes to the results (Supplementary Table 1).

4.4. Discussion

We assessed the association between short-term exposure to particulate matter ($PM_{2.5}$) from satellite observations and respiratory outcomes in children in India. The result showed that short-term exposure to $PM_{2.5}$ increased the risk of developing AURI and ALRI, with higher odds for ALRI in children under five years of age in India. The results are not modified by sex or solid fuel use.

Although we found a stronger association for ALRI, the cubic spline analysis suggests that the odds for ALRI began to lower at above 80 μg/m^3, however, remained significant. In contrast, the odds of AURI slowly increased with increasing levels of $PM_{2.5}$ in children under five years of age living in India. Despite the quartile level associations

and cubic models do not fairly match the outcomes, it seems that there is a dose-response relationship with increasing levels of $PM_{2.5}$ and AURI and ALRI.

India holds a large burden for chronic respiratory diseases (Collaborators IS-LDBIC 2018). Outdoor air pollution is known to affect a child's upper and lower respiratory tract (Romieu et al. 2002). A meta-analysis of the association between fine particulate matter and respiratory tract diseases showed that children from North America, Europe, and Asia exposed to $PM_{2.5}$ experienced a higher incidence of cough, wheezing, and LRI which was similar in our study (Liu et al. 2017), in which we defined AURI as coughing and similarly found associations for AURI and ALRI. Furthermore, our cubic spline for AURI and ALRI was similar to that of Kim et al. (2020). However, in their study that included 15 regions in the Republic of Korea, short-term exposure to $PM_{2.5}$ was not associated with ALRI (Kim et al. 2020). The reason behind this can be explained by the maximum levels of $PM_{2.5}$ in our study which was significantly higher than the maximum levels of $PM_{2.5}$ observed in the study by Kim et al. (2020), 133,7 $\mu g/m^3$, and 40 $\mu g/m^3$, respectively. Indeed, higher levels of $PM_{2.5}$ contributed to the development of respiratory tract diseases in children such as ALRI (Liu et al. 2017). Furthermore, Horne et al. (2018) in a case-crossover study of 112,467 children aged 0 to 2 years from the Wasatch Front region of Utah, with similar levels of $PM_{2.5}$ to ours, observed an increased odds of ALRI with short-term exposure to $PM_{2.5}$ (Horne et al. 2018). Children living in highly polluted areas are at risk of developing an impaired nasal epithelium and weakening of mucociliary defense making them more likely to become susceptible to particulate matter in the air as the function of nasal epithelium becomes compromised to protect the lower respiratory tract (Salvi 2007).

There are strengths to our study. First, we used a large nationally representative

survey with a high response rate of 98%. Second, solid-fuel use did not modify the association between exposure to levels of $PM_{2.5}$ and the outcomes, which was the main contributor for acute respiratory infection in children in previous studies (Suryadhi et al. 2019, Smith et al. 2000). Furthermore, there are several limitations of our study. First, the measurement of levels of $PM_{2.5}$ represented the cluster level, potentially a source of bias such as misclassification of exposure. However, this misclassification tends to be non-differential moving the effect towards the null (Rothman 2012). Second, we relied on self-reported health outcomes for AURI and ALRI that could inflict maternal recall bias. However, responses relating to AURI and ALRI were recalled 2 weeks before the survey, unlikely resulting in a major bias. Besides, this type tends to be a non-differential bias (Rothman 2012). Third, we were unable to establish a causal inference due to the nature of the cross-sectional study. Fourth, we found that the distribution levels of $PM_{2.5}$ were very high across India. This could underestimate the effect of $PM_{2.5}$ on AURI and ALRI. Fifth, "poorer" and "poorest" groups could be underestimated in the socioeconomic status of the subjects in this study which can be a source of selection bias. However, when we included urban and rural subjects in the analysis, results remained (Supplementary Table 2).

4.5. Conclusions

In conclusion, children under five years of age exposed to high levels of $PM_{2.5}$ had increased odds of AURI and ALRI. Although the association appeared stronger for ALRI, the association started to lower at above 80 $\mu g/m^3$. Mitigation efforts must continue to be implemented and at higher restrictions in India to ensure safe levels of air for children, pregnant women, older residents, and the population as air pollution may contribute to

significant DALYs and mortality for India.

Chapter 5 General Conclusion

We assessed the association between exposure to air pollution and the health of children in Indonesia. In the first study, we evaluated associations between air pollution (NO_2 and SO_2) and health in children aged 0-3 years in Indonesia. We assigned participants provincial levels of NO_2 and SO_2 and examined associations with LBW, infant death, neonatal death, and acute ARI. An IQR increase in mean NO_2 exposure associated with an increased risk of ARI by 18%. The association for ARI was confirmed by assessing the quartile exposure categories. In contrast, SO_2 was not associated with the risk of any of the studies child health outcomes. In the second study, we assessed the combined effect of household air pollution from solid fuel use and from environmental tobacco smoke and child health outcomes in Indonesia. We observed an increased risk of LBW, neonatal death, infant death, and acute lower respiratory infection. Children exposed to high levels of pollution from solid fuel use were associated with an increased risk of low birth weight, neonatal death, infant death, and acute lower respiratory infection. Exposure to environmental tobacco smoke was associated with an increased risk of acute lower respiratory infection. A combined exposure to HAP from solid fuel use and ETS was more detrimental than exposure to each pollution source alone. The findings from our study showed that exposure to indoor and outdoor air pollution associated with child-health outcomes since early childhood.

TABLES

Table 1. Characteristics of people who died from all causes, excluding external causes, in yokkaichi, Japan, 1972-1991.

	n=29839
Mean age ,year (SD)	69.92(17.8)
Women, n(%)	14372(48.17)
Tyes of mortality, n(%)	
Cardiovascular disease	13017(43.62)
Ischemic heart diseaes	1972(6.61)
Cerebrovascular disease	6171(20.68)
Respiratory disease	2696(9.04)
Pneumonia	1567(5.25)
COPD and asthma	753(2.52)
Number of mortality, (%)	29,839
Firs half of the study period (1972 to 1981)	13876(22.72)
Second half of the study period(1982 to 1991)	15963(22.75)
SO2consentration, ppb	
Median	9.7
25th to 75th	6.8 ,14.3
5th to 95th	35.4, 28.6

COPD: chronic obstructive pulmonary disease; ppb:parts per billion; SD: standard deviation; SO_2: sulfur dioxide

Table 2. Adjusted ods ratios* per intequartile range nicrease in SO_2concentration from 1972-1991, Yokkaichi Japan

	OR(95%CI)				
	lag 0	lag 1	lag 2	lag 3	lag 4
All-causes of death	1.01(0.98, 1.03)	1.01(0.99, 1.03)	1.02(1, 1.04)	1.01(0.99, 1.04)	1.02(0.99, 1.05)
Cardiovascular disease	0.99(0.96, 1.03)	1.01(0.97, 1.04)	1.03(0.99, 1.06)	1(0.96, 1.04)	1.02(0.97, 1.06)
Ischemic heart disease	0.99(0.9, 1.09)	1(0.91, 1.1)	1.1(1.01, 1.2)	0.99(0.89, 1.1)	1.05(0.94, 1.18)
Cerebrovascular disease	0.98(0.93, 1.03)	1.05(1, 1.1)	1.02(0.97, 1.07)	1.02(0.96, 1.08)	1.02(0.97, 1.08)
Respiratory disease	1.01(0.93, 1.1)	0.95(0.87, 1.03)	0.98(0.91, 1.06)	0.97(0.89, 1.07)	0.97(0.87, 1.07)
Pneumonia	1.01(0.89, 1.14)	1.01(0.9, 1.13)	1.04(0.93, 1.17)	1.01(0.89, 1.15)	1.03(0.9, 1.19)
COPD and asthma	1.02(0.88, 1.18)	0.89(0.77, 1.03)	0.91(0.8, 1.04)	0.94(0.8, 1.1)	0.9(0.77, 1.07)
First half of the study period (From 1972 to 1981)					
All-causes of death	0.99(0.96, 1.02)	0.99(0.96, 1.01)	1(0.98, 1.03)	0.98(0.96, 1.01)	0.99(0.96, 1.01)
Cardiovascular disease	0.98(0.94, 1.03)	0.99(0.95, 1.03)	1.01(0.97, 1.05)	0.98(0.94, 1.03)	0.98(0.94, 1.03)
Ischemic heart disease	0.99(0.88, 1.1)	1.02(0.92, 1.14)	1.13(1.02, 1.25)	1.01(0.9, 1.13)	1.01(0.9, 1.13)
Cerebrovascular diseas	0.97(0.91, 1.03)	1.02(0.97, 1.08)	1(0.95, 1.06)	1(0.94, 1.06)	1(0.94, 1.06)
Respiratory disease	0.95(0.86, 1.06)	0.91(0.82, 1.01)	0.92(0.84, 1.02)	0.91(0.81, 1.02)	0.91(0.82, 1.02)
Pneumonia	1.01(0.86, 1.19)	0.94(0.81, 1.09)	0.93(0.8, 1.08)	0.97(0.82, 1.14)	0.97(0.83, 1.14)
COPD and asthma	0.91(0.77, 1.07)	0.88(0.74, 1.03)	0.88(0.76, 1.03)	0.86(0.72, 1.03)	0.87(0.73, 1.03)
Second half of the study period (From 1982 to 1991)					
All-causes of death	1.06(1.01, 1.11)	1.07(1.02, 1.12)	1.05(1.01, 1.1)	1.09(1.03, 1.15)	1.08(1.03, 1.14)
Cardiovascular disease	1.02(0.95, 1.1)	1.06(0.99, 1.14)	1.08(1.01, 1.16)	1.06(0.97, 1.15)	1.05(0.98, 1.14)
Ischemic heart disease	0.96(0.78, 1.17)	0.94(0.78, 1.15)	1.05(0.87, 1.26)	0.93(0.75, 1.16)	0.93(0.76, 1.15)
Cerebrovascular diseas	1(0.89, 1.12)	1.12(1.01, 1.25)	1.12(1.12, 1.01)	1.08(0.96, 1.23)	1.08(0.96, 1.21)
Respiratory disease	1.14(0.98, 1.33)	1.04(0.89, 1.21)	1.07(0.97, 1.19)	1.12(0.95, 1.33)	1.11(0.95, 1.31)
Pneumonia	1(0.82, 1.21)	1.12(0.93, 1.35)	1.03(1.45, 1.08)	1.08(0.88, 1.34)	1.08(0.88, 1.31)
COPD and asthma	1.61(1.17, 2.22)	0.99(0.71, 1.38)	1.05(0.78, 1.42)	1.39(0.97, 1.99)	1.36(0.97, 1.92)

*Adjusted for ambient temperature (df=5), humidity (df=3), and holidays. Interquartile range=6.9ppb.

CI:confidence interval; COPD: chronic obstructive pulmanary disease; df: degrees of freedom; OR: odds ratio; ppb: parts per billion; SO_2: sulfur dioxide

Table 3. Adjusted odds ratio* for mortality outcomes at different levels of SO_2, compared with first quartile as reference

	OR(95%CI)				
	lag0	lag1	lag2	lag01	lag02
All-causes of death					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	1.04(0.97, 1.04)	1.04(1, 1.08)	1.04(1, 1.08)	1.03(0.99, 1.07)	1.05(1.01, 1.09)
Q3	1.04(1, 1.09)	1.04(1, 1.09)	1.02(0.98, 1.06)	1.05(1.01, 1.1)	1.09(1.05, 1.15)
Q4	1.02(0.96, 1.08)	1.07(1.01, 1.13)	1.06(1, 1.12)	1.09(1.02, 1.16)	1.14(1.06, 1.21)
Cardiovascular disease					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	1.02(0.96, 1.08)	1.05(0.99, 1.12)	1.03(0.97, 1.09)	1.02(0.97, 1.09)	1.01(0.96, 1.08)
Q3	1.01(0.95, 1.08)	1.02(0.96, 1.09)	1.05(0.99, 1.12)	1.02(0.95, 1.09)	1.09(1.01, 1.17)
Q4	1.02(0.93, 1.12)	1.08(0.99, 1.18)	1.04(0.96, 1.13)	1.09(0.99, 1.2)	1.12(1.01, 1.23)
Ischemic heart disease					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	1.07(0.91, 1.25)	1.07(0.92, 1.25)	1.08(0.93, 1.26)	1.1(0.94, 1.29)	1.1(0.94, 1.29)
Q3	0.99(0.83, 1.18)	0.98(0.83, 1.17)	1.1(0.93, 1.3)	1.01(0.85, 1.21)	1.13(0.94, 1.35)
Q4	1.09(0.86, 1.37)	1.03(0.83, 1.29)	1.11(0.9, 1.38)	1.11(0.87, 1.41)	1.17(0.91, 1.52)
Cerebrovascular disease					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0.97(0.89, 1.06)	1.1(1.01, 1.21)	1.04(0.95, 1.13)	1.06(0.97, 1.16)	1.05(0.96, 1.15)
Q3	0.98(0.89, 1.08)	1.1(1, 1.21)	1.06(0.97, 1.17)	1.06(0.95, 1.17)	1.06(0.96, 1.18)
Q4	0.96(0.84, 1.09)	1.16(1.03, 1.32)	0.96(0.85, 1.09)	1.11(0.97, 1.27)	1.11(0.96, 1.28)
Respiratory disease					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	1.02(0.9, 1.16)	1.02(0.9, 1.15)	1.11(0.98, 1.26)	1(0.88, 1.14)	1.05(0.92, 1.19)
Q3	1.08(0.94, 1.25)	1.02(0.89, 1.17)	1.11(0.97, 1.27)	1(0.86, 1.16)	1.06(0.91, 1.23)
Q4	1.08(0.89, 1.32)	1.07(0.88, 1.3)	0.78(0.89, 1.28)	1.07(0.87, 1.31)	1.14(0.91, 1.42)
Pneumonia					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	0.95(0.81, 1.11)	1.02(0.87, 1.2)	1.19(1.02, 1.4)	1.04(0.89, 1.23)	1.07(0.91, 1.26)
Q3	0.96(0.8, 1.16)	1.07(0.89, 1.27)	1.25(1.05, 1.49)	0.96(0.8, 1.16)	1.05(0.87, 1.27)
Q4	0.95(0.74, 1.23)	1.05(0.81, 1.35)	1.19(0.94, 1.52)	0.99(0.75, 1.31)	1.12(0.84, 1.51)
COPD and asthma					
Q1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Q2	1.35(1.04, 1.76)	0.89(0.69, 1.15)	0.88(0.68, 1.13)	1.01(0.78, 1.31)	1(0.77, 1.29)
Q3	1.48(1.11, 1.98)	0.9(0.68, 1.19)	0.9(0.69, 1.18)	1.1(0.83, 1.46)	1.11(0.83, 1.49)
Q4	1.45(0.99, 2.12)	1.1(0.76, 1.58)	0.94(0.67, 1.31)	1.2(0.81, 1.77)	1.24(0.81, 1.91)

* Adjusted for ambient temperature (df=4), humidity (df=3), and holidays.
CI: confidence interval; COPD:chronic obstructive pulmonary disease; df=degrees of freedom;
OR: odds ratio; Q1: first quartile; Q2: second quartile; Q3: third quartile; Q4:fourth quartile; dioxide
ref: reference; SO2: sulfur dioxide.

Tbale 4. Adjusted odds ratios* per interquarile range increase in SO2 during the second half of the study period (1982-1991) obtained from a two-pollutant model including SO2 and suspended particulate matter or nitrogen dioxide

	OR(95%)				
	lag0	lag1	lag2	lag01	lag02
SPM adjustment					
All-causes of death	1.05(0.96, 1.14)	1.06(1, 1.13)	1.06(1.01, 1.12)	1.09(1.01, 1.19)	1.09(1.01, 1.17)
Crdiovascular disease	1.07(0.94, 1.22)	1.11(1.01, 1.22)	1.09(1, 1.18)	1.16(1.02, 1.32)	1.15(1.02, 1.3)
Respiratory disease	1.15(0.88, 1.5)	1.02(0.84, 1.23)	1.15(0.97, 1.35)	1.1(0.84, 1.43)	1.09(0.85, 1.4)
NO2 ajustment					
All-causes of disease	1.07(0.99, 1.15)	1.05(1, 1.1)	1.05(1.01, 1.1)	1.07(1.01, 1.14)	1.07(1.01, 1.13)
Crdiovascular disease	1.04(0.93, 1.17)	1.06(0.98, 1.14)	1.08(1, 1.15)	1.07(0.97, 1.18)	1.07(0.97, 1.17)
Respiratory disease	1.2(0.94, 1.53)	1.03(0.88, 1.2)	1.14(0.99, 1.31)	1.11(0.9, 1.36)	1.1(0.9, 1.34)

*Adjutsted for ambient temperature (df=5), humidity (df=3), and holidays. Interquartile range=6.9 ppb.

CI: confidence interval: COPD:chronic obstructive pilmonary disease; df: degrees of freedom; NO2:nitrogen dioxide; OR: odds ratio; ppb: parts per billion; SO2: sulfur dioxide; SPM: suspended particulare matter

Table 5. Demographic characteristics of children included in the study (N = 36,842)

Variable	Total
Child Characteristics	
Age, years (mean±SD)	4.8±3.0
Sex, n (%)	
Boy	19139(52.0)
Girl	17703(48.1)
Parents Characteristics	
Mothers age (mean±SD)	32.5±6.8
Mothers Education, n (%)	
No education	1480(4.0)
Primary school	12820(34.8)
Secondary school	18367(49.9)
Higher school	4175(11.3)
Air Pollution	
Type of cooking fuel[a], n (%)	
Solid fuel	
Coal, lignite	11(0.03)
Charcoal	267(0.7)
Wood	15000(40.7)
Straw/shrubs/grass	16(0.04)
Non-solid fuel	
Electricity	64(0.2)
Lpg/Natural gas	15367(41.7)
Biogas	67(0.2)
Kerosene	5934(16.1)
Other[c]	19(0.05)
No food cooked in house[c]	73(0.2)
Missing[c]	24(0.07)
Frequency of household members smoking inside the house[b]	
Daily	25824(70.1)
Weekly	2408(6.5)
Less than monthly	759(2.1)
Monthly	1030(2.8)
Never	6784(18.4)
Missing[d]	37(0.1)

SD, standard deviation

[a] We characterized children whose families used coal, lignite, charcoal, wood, or straw/shrubs/grass as highly exposed to household air pollution.

[b] We characterized children whose families smoked daily inside the house as highly exposed to environmental tobacco smoke.

[c] Excluded from the analysis of household air pollution from solid-fuel use.

[d] Excluded from the analysis of environmental tobacco smoke.

Table 6. Incidence and odds ratios (ORs) of household air pollution from solid-fuel use and child health outcomes in Indonesia (N = 36,726)

	Case/N	OR (95% CI)		
		Crude	Adjusted[a]	Adj. for ETS[a]
Low birth weight	951 / 14,475	1.90 (1.66 - 2.18)	1.62 (1.38 - 1.90)	1.61 (1.37 - 1.89)
Neonatal death	717 / 36,726	1.72 (1.46 - 2.01)	1.38 (1.14 - 1.67)	1.37 (1.13 - 1.66)
Infant death	1,264 / 36,726	1.89 (1.67 - 2.14)	1.41 (1.22 - 1.64)	1.41 (1.22 - 1.63)
Acute upper respiratory infection	5,740 / 16,537	1.06 (0.99 - 1.13)	1.01 (0.93 - 1.09)	1.00 (0.93 - 1.09)
Acute lower respiratory infection	1,872 / 16,515	1.32 (1.19 - 1.45)	1.23 (1.09 - 1.38)	1.22 (1.08 - 1.37)

[a] Adjusted for child's age, child's sex, mother's age, mother's education, and residential area.

CI, confidence interval; ETS, environmental tobacco smoke.

Table 7. Incidence and adjusted odds ratios (ORs) for the combined effect of household air pollution from solid-fuel use (HAP) and environmental tobacco smoke (ETS) and child health outcomes in Indonesia (N = 36,709)

		OR (95%CI)			
	Case/N	No exposure (n:7349)	High HAP[a] (n:3597)	High ETS[a] (n:14075)	Both HAP and ETS[a] (n:11688)
Low birth weight	949 / 14,468	Ref.	1.38 (1.03 - 1.86)	1.01 (0.82 - 1.23)	1.70 (1.36 - 2.12)
Neonatal death	716 / 36,709	Ref.	1.76 (1.26 - 2.46)	1.31 (1.00 - 1.71)	1.66 (1.25 - 2.21)
Infant death	1,263 / 36,709	Ref.	1.41 (1.09 - 1.83)	1.14 (0.93 - 1.39)	1.60 (1.29 - 1.97)
Acute upper respiratory infection	5,738 / 16,530	Ref.	1.05 (0.91 - 1.21)	1.05 (0.96 - 1.16)	1.04 (0.94 - 1.16)
Acute lower respiratory infection	1,872 / 16,508	Ref.	1.21 (0.98 - 1.50)	1.12 (0.97 - 1.29)	1.36 (1.16 - 1.61)

[a] Adjusted for child's age, child's sex, mother's age, mother's education, and residential area.

CI, confidence interval.

Table 8. Incidence and odds ratios (ORs) of environmental tobacco smoke exposure and child health outcomes in Indonesia (N = 36,805)

	Case/N	OR (95%CI)		
		Crude	Adjusted[a]	Adj. for HAP[a]
Low birth weight	954 / 14,518	1.20 (1.03 - 1.40)	1.11 (0.95 - 1.30)	1.09 (0.93 - 1.27)
Neonatal death	719 / 36,805	1.24 (1.03 - 1.49)	1.13 (0.94 - 1.36)	1.11 (0.92 - 1.33)
Infant death	1,266 / 36,805	1.28 (1.11 - 1.47)	1.16 (1.00 - 1.33)	1.13 (0.98 - 1.31)
Acute upper respiratory infection	5,752 / 16,577	1.06 (0.98 - 1.14)	1.03 (0.96 - 1.11)	1.03 (0.96 - 1.11)
Acute lower respiratory infection	1,877 / 16,555	1.18 (1.05 - 1.32)	1.13 (1.01 - 1.27)	1.12 (1.00 - 1.26)

[a] Adjusted for child's age, child's sex, mother's age, mother's education, and residential area.

CI, confidence interval; HAP, household air pollution from solid-fuel use.

Table 9. Sociodemographic characteristics of subjects in India (N=55,118)

	Total
Child:	
Age	2.1±1.4
Sex	
Male	25514(52.3)
Female	23263(47.7)
Mother:	
Education	
Higher	9643(19.8)
Secondary	25385(52.0)
Primary	5292(10.9)
No education	8457(17.3)
Wealth index	
Richest	17441(35.8)
Richer	14711(30.2)
Middle	9273(19.0)
Poorer	4987(10.2)
Poorest	2365(4.9)
Solid-fuel for cooking	
Solid-fuel	13265(27.2)
Non solid-fuel	35487(72.8)
Population density	2264.4±5392.5

Table 10. Odds ratios and 95% Confidence Intervals for the Association between Exposure to Particulate Matter ($PM_{2.5}$) levels and AURI and ALRI in India during 2015-2016.

	Case/N	Prevalence	OR (95%CI)		
			Crude	Adjusted[a]	Fully-Adjusted[b]
AURI					
per 10 μg/m^3	6341/55118	11.5	1.02(1.01 - 1.03)	1.02(1.01 - 1.03)	1.02(1.02 - 1.03)
Quartiles:					
Q1 (8.55-43.75) μg/m^3	1652/14439	11.4	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2 (43.80-59.80) μg/m^3	1405/13932	10.1	0.88(0.81 - 0.95)	0.89(0.82 - 0.96)	0.89(0.82 - 0.96)
Q3 (59.80-94.10) μg/m^3	1513/12529	12.1	1.05(0.98 - 1.14)	1.06(0.98 - 1.15)	1.06(0.98 - 1.15)
Q4 (94.15-133.70) μg/m^3	1615/12989	12.4	1.10(1.02 - 1.19)	1.12(1.03 - 1.21)	1.13(1.04 - 1.23)
ALRI					
per 10 μg/m^3	2824/55100	5.1	1.05(1.03 - 1.06)	1.05(1.03 - 1.06)	1.05(1.03 - 1.06)
Quartiles:					
Q1 (8.55-43.75) μg/m^3	609/14434	4.2	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2 (43.80-59.80) μg/m^3	628/13928	4.5	1.08(0.96 - 1.21)	1.09(0.96 - 1.22)	1.09(0.96 - 1.22)
Q3 (59.80-94.10) μg/m^3	737/12520	5.9	1.42(1.27 - 1.59)	1.41(1.26 - 1.59)	1.41(1.26 - 1.59)
Q4 (94.15-133.70) μg/m^3	768/12989	5.9	1.44(1.28 - 1.61)	1.44(1.28 - 1.62)	1.44(1.28 - 1.62)

OR: Odds ratio

[a] Adjusted for child's age, child's sex, mothers education, and mothers smoking status

[b] Included covariates in [a] and further adjusted for population density.

Table 11. Effect modification of the association between AURI and ALRI and exposure to particulate matter ($PM_{2.5}$) levels in India during 2015-2016.

Characteristics	Subgroups	Case/N	Prevalence	ORs (95% Confidence Intervals)	*p*-interaction
AURI:					
Sex	Male	3411/28925	11.79	1.03(1.01 - 1.04)	0.373
	Female	2930/26193	11.19	1.02(1.01 - 1.04)	
Solid-fuel	Yes	1829/15094	12.12	1.03(1.01 - 1.05)	0.907
	No	4509/39996	11.27	1.02(1.01 - 1.03)	
ALRI:					
Sex	Male	1559/28914	5.39	1.06(1.04 - 1.07)	0.144
	Female	1265/26186	4.83	1.04(1.02 - 1.06)	
Solid-fuel	Yes	852/15090	5.65	1.06(1.03 - 1.09)	0.545
	No	1971/39982	4.93	1.05(1.03 - 1.06)	

OR: odds ratio

Adjusted for child's age, child's sex, mother's education, mothers smoking status, and population density

SUPPLEMWNTARY TABLES

Supplementary 1. Odds ratios and 95% Confidence Intervals for the Association between Exposure to Particulate Matter ($PM_{2.5}$) levels and AURI and ALRI in India during 2015-2016 adjusted using wealth index instead of mother's education.

	Case/N	Prevalence	OR (95%CI)		
			Crude	Adjusted[a]	Fully-Adjusted[b]
AURI					
per 10 µg/m^3	6341/55118	11.5	1.02 (1.01 - 1.03)	1.02 (1.01 - 1.03)	1.03 (1.02 - 1.04)
Quartiles:					
Q1 (8.55-43.75) µg/m^3	1652/14439	11.4	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2 (43.80-59.80) µg/m^3	1405/13932	10.1	0.88 (0.81 - 0.95)	0.89 (0.82 - 0.96)	0.91 (0.84 - 0.98)
Q3 (59.80-94.10) µg/m^3	1513/12529	12.1	1.05 (0.98 - 1.14)	1.06 (0.98 - 1.15)	1.08 (1.00 - 1.17)
Q4 (94.15-133.70) µg/m^3	1615/12989	12.4	1.10 (1.02 - 1.19)	1.12 (1.03 - 1.21)	1.14 (1.06 - 1.24)
ALRI					
per 10 µg/m^3	2824/55100	5.1	1.05 (1.03 - 1.06)	1.05 (1.03 - 1.06)	1.05 (1.04 - 1.06)
Quartiles:					
Q1 (8.55-43.75) µg/m^3	609/14434	4.2	1 (Ref.)	1 (Ref.)	1 (Ref.)
Q2 (43.80-59.80) µg/m^3	628/13928	4.5	1.08 (0.96 - 1.21)	1.09 (0.96 - 1.22)	1.11 (0.98 - 1.24)
Q3 (59.80-94.10) µg/m^3	737/12520	5.9	1.42 (1.27 - 1.59)	1.41 (1.26 - 1.59)	1.44 (1.28 - 1.62)
Q4 (94.15-133.70) µg/m^3	768/12989	5.9	1.44 (1.28 - 1.61)	1.44 (1.28 - 1.62)	1.46 (1.29 - 1.64)

OR: Odds ratio

[a] Adjusted for child's age, child's sex, wealth index, and mothers smoking status

[b] Included covariates in [a] and further adjusted for population density.

Supplementary 2. Odds ratios and 95% Confidence Intervals for the Association between Exposure to Particulate Matter ($PM_{2.5}$) levels and AURI and ALRI in India during 2015-2016 (Rural and Urban subjects)

	Case/N	Prevalence	OR (95%CI)		
			Crude	Adjusted[a]	Fully-Adjusted[b]
AURI					
per 10 µg/m^3	26630/231004	11.5	1.02(1.01 - 1.02)	1.02(1.02 - 1.03)	1.03(1.02 - 1.03)
Quartiles:					
Q1 (6.90-44.95) µg/m^3	6734/57601	11.7	1(Ref.)	1(Ref.)	1(Ref.)
Q2 (45.00-61.50) µg/m^3	5790/55543	10.4	0.88(0.85 - 0.92)	0.91(0.87 - 0.95)	0.91(0.87 - 0.95)
Q3 (61.55-95.85) µg/m^3	6524/56749	11.5	0.98(0.95 - 1.02)	1.02(0.99 - 1.06)	1.03(0.99 - 1.07)
Q4 (95.90-139.00) µg/m^3	7261/58304	12.5	1.08(1.04 - 1.12)	1.14(1.10 - 1.19)	1.15(1.11 - 1.20)
ALRI					
per 10 µg/m^3	12658/230924	5.5	1.05(1.04 - 1.05)	1.05(1.04 - 1.06)	1.05(1.04 - 1.06)
Quartiles:					
Q1 (6.90-44.95) µg/m^3	2662/57581	4.6	1(Ref.)	1(Ref.)	1(Ref.)
Q2 (45.00-61.50) µg/m^3	2794/55527	5.0	1.10(1.04 - 1.16)	1.12(1.05 - 1.18)	1.12(1.05 - 1.18)
Q3 (61.55-95.85) µg/m^3	3332/56720	5.9	1.29(1.22 - 1.36)	1.32(1.25 - 1.40)	1.32(1.25 - 1.40)
Q4 (95.90-139.00) µg/m^3	3719/58289	6.4	1.41(1.34 - 1.49)	1.46(1.39 - 1.55)	1.47(1.39 - 1.55)

OR: Odds ratio

[a] Adjusted for child's age, child's sex, wealth index, residency, and mothers smoking status

[b] Included covariates in [a] and further adjusted for population density.

FIGURES

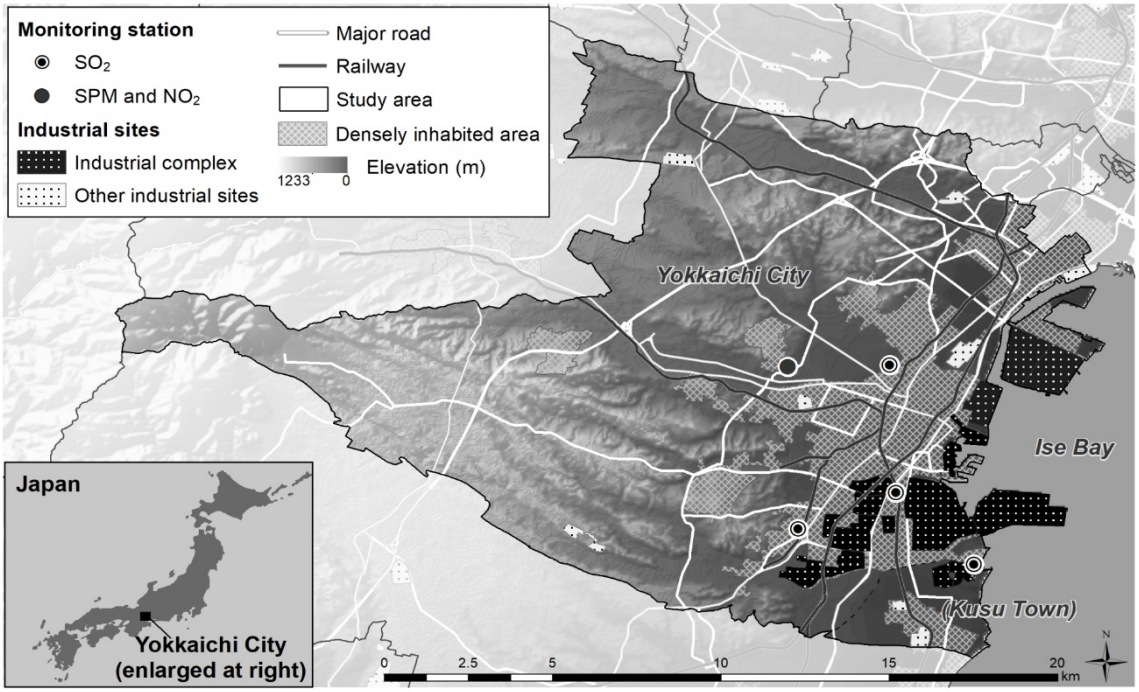

Figure 1. Map of the study area.

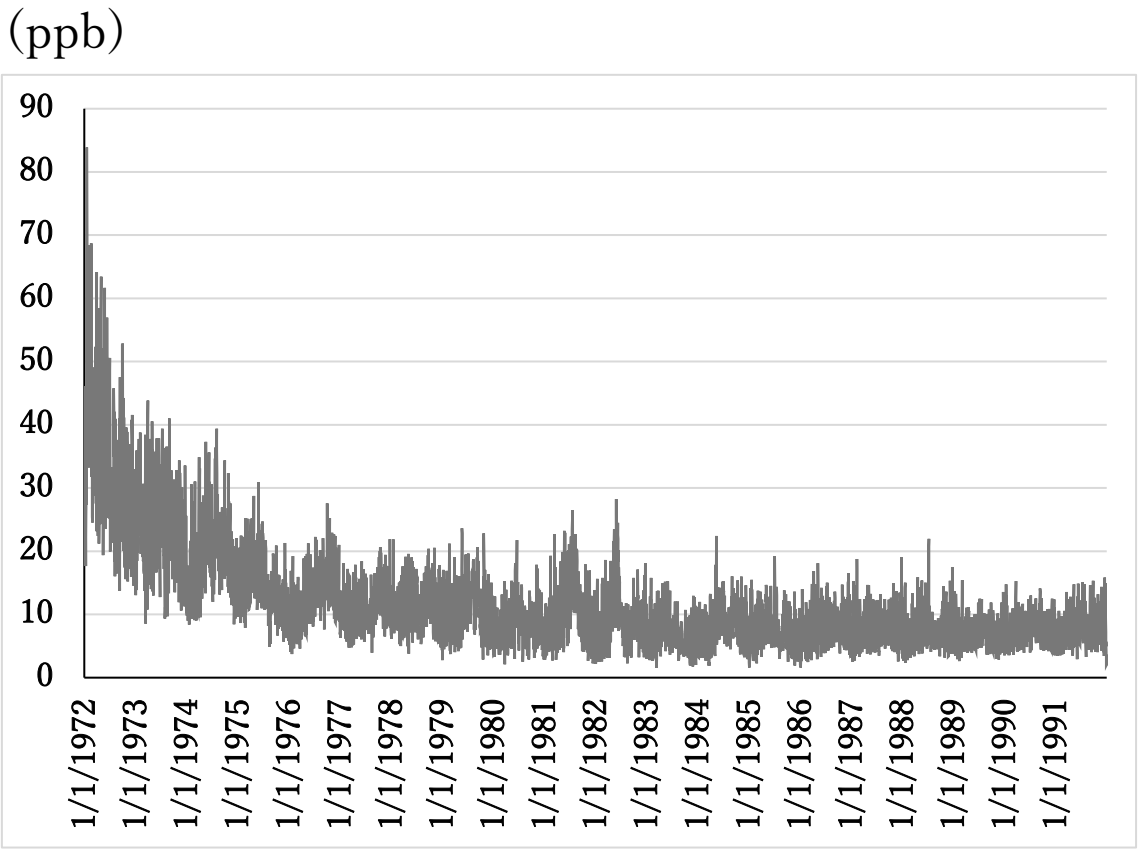

Figure 2. Trends in sulfur dioxide concentrations in Yokkaichi from 1972–1991.

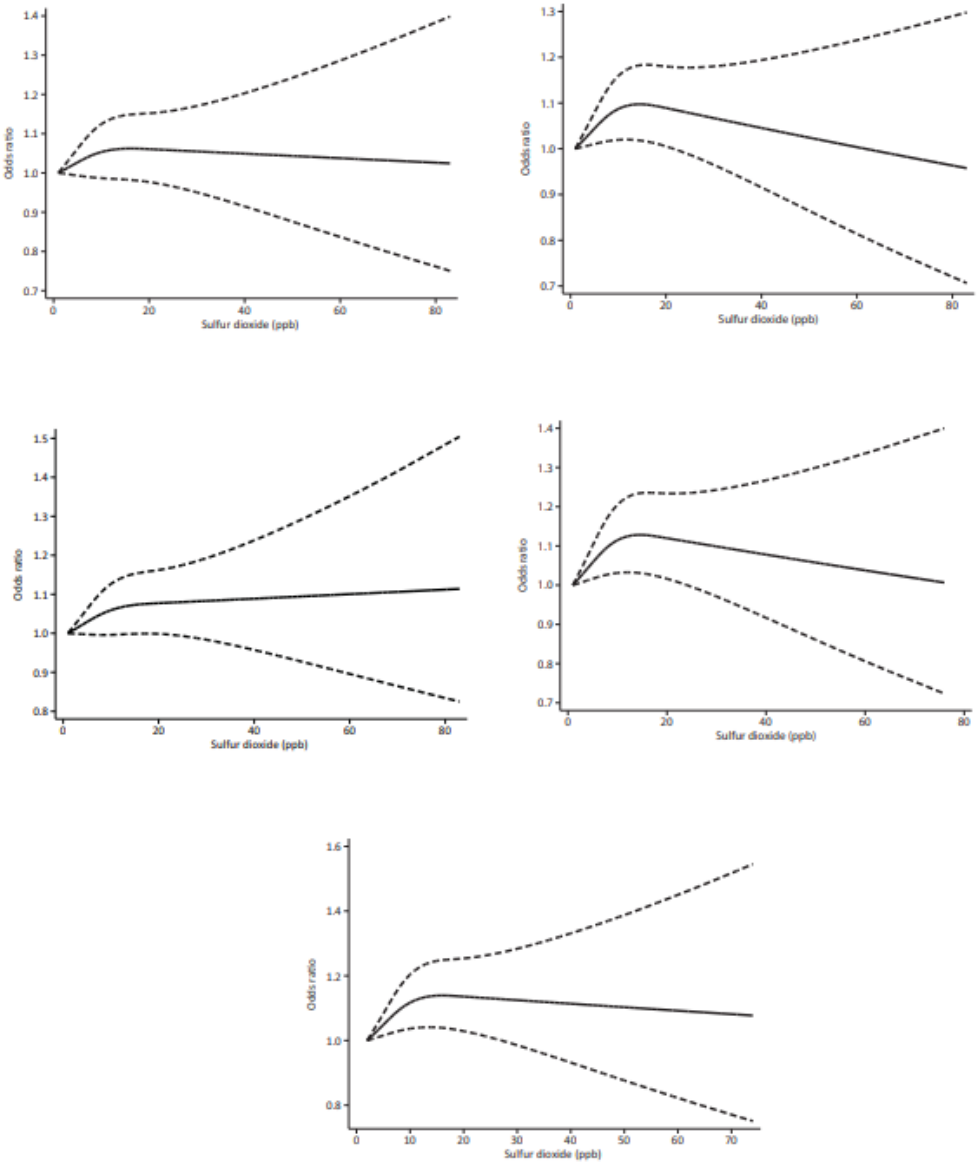

Figure 3. Predicted shape of the concentration-response relationship between sulfur dioxide exposure and all-cause mortality. The adjusted odds ratios and their 95% confidence intervals for all-cause mortality across the range of the observed sulfur dioxide exposure are shown for: (a) same-day exposure (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).

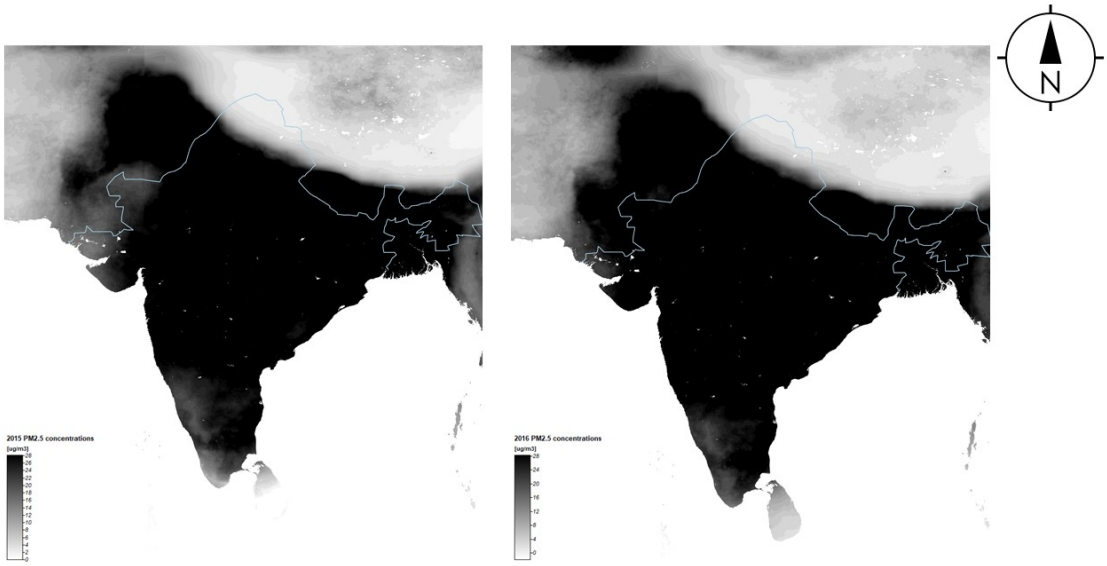

Figure 4. The distribution of particulate matter ($PM_{2.5}$) levels in 2015-2016 in India

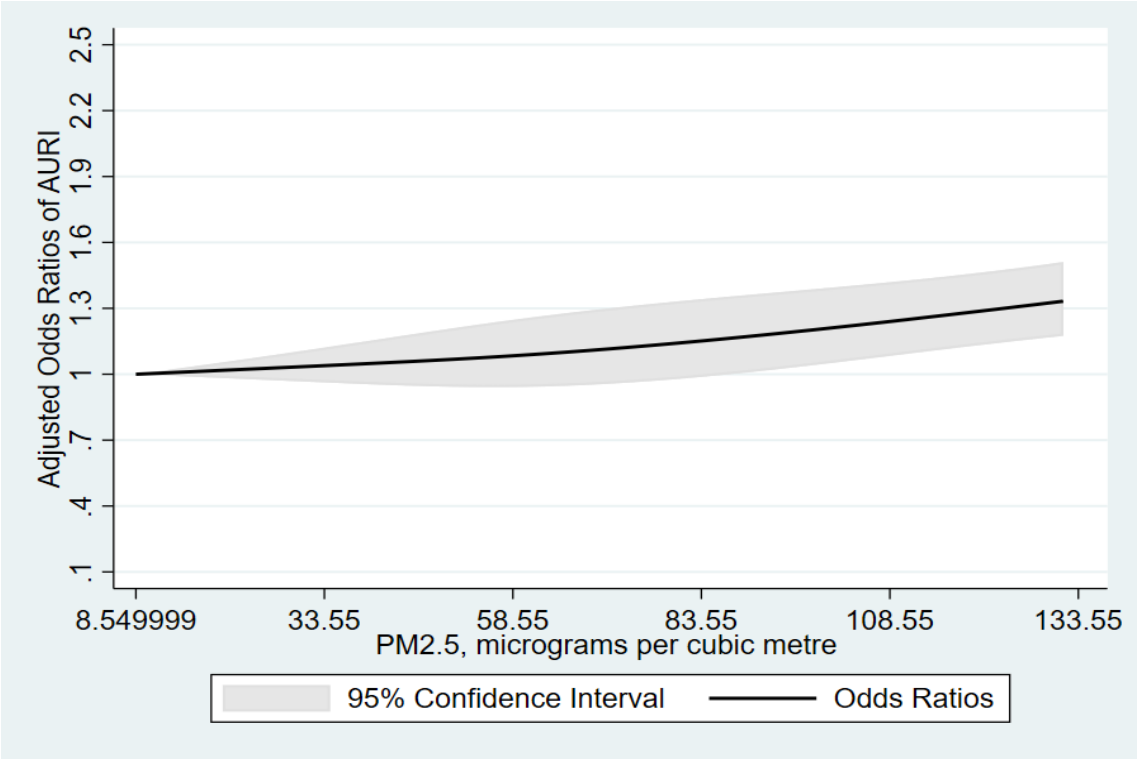

Figure 5. Restricted cubic spline of the association between exposure to particulate matter ($PM_{2.5}$) and the prevalence of AURI adjusted for child's age, child's sex, mother's education, mothers smoking status, and population density.

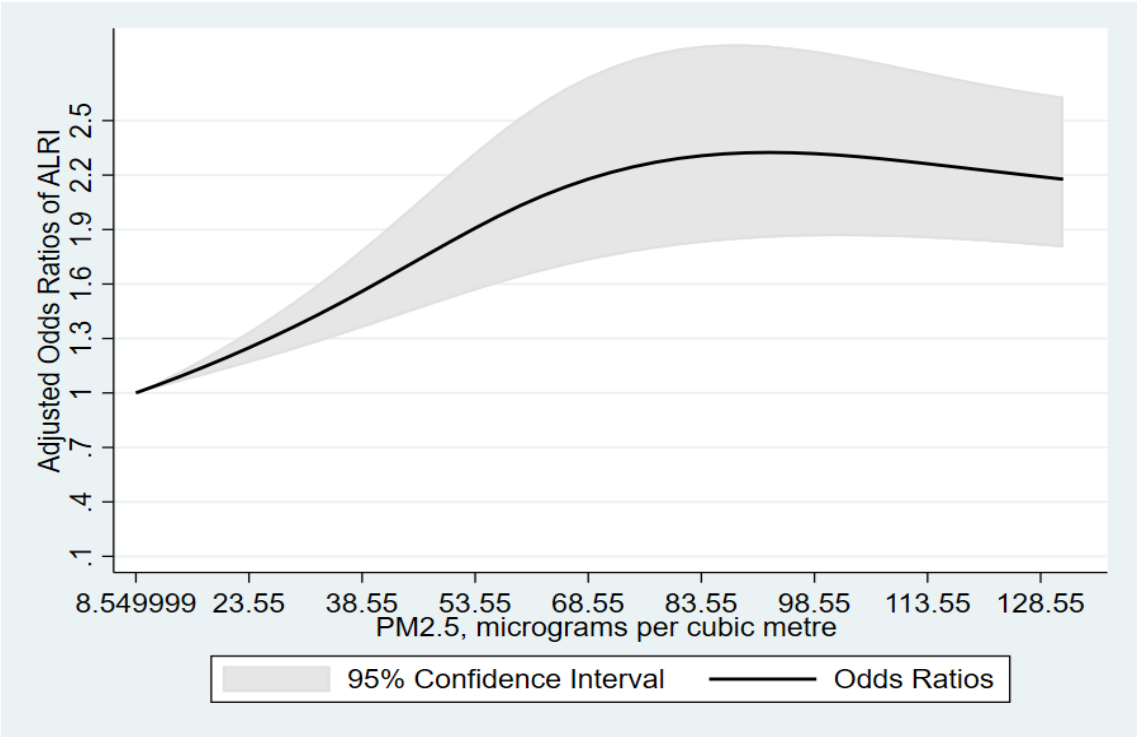

Figure 6. Restricted cubic spline of the association between exposure to particulate matter (PM2.5) and the prevalence of ALRI adjusted for child's age, child's sex, mother's education, mothers smoking status, and population density.

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