Abstract

Background: Long-term exposure to air pollution is linked with increased risk of adverse health outcomes, but the evidence for the association between nitrogen dioxide (NO_2) and mortality is weak because of the inadequate adjustment of potential confounders and limited spatial resolution of the exposure assessment. Moreover, there are concerns about the independent effects of NO_2. Therefore, we examined the association between NO_2 long-term exposure and all-cause and cause-specific mortality.

Methods: We included participants who were enrolled in health checkups in Okayama City, Japan, in 2006 or 2007 and were followed until 2016. We used a land-use regression model to estimate the average NO_2 concentrations from 2006 to 2007 and allocated them to the participants. We estimated hazard ratios (HRs) for a 10-$\mu g/m^3$ increase in NO_2 levels for all-cause or cause-specific mortality using Cox proportional hazard models.

Results: After excluding the participants who were assigned with outlier exposures, a total of 73,970 participants were included in the analyses. NO_2 exposure was associated with increased risk of mortality and the HRs and their confidence intervals were 1.06 (95% CI: 1.02, 1.11) for all-cause, 1.02 (0.96, 1.09) for cardiopulmonary, and 1.36 (1.14, 1.63) for lung cancer mortality. However, the elevated risks became equivocal after the adjustment for fine particulate matter except lung cancer.

Conclusion: Long-term exposure to NO_2 was associated with increased risk of all-cause, cardiopulmonary, and lung cancer mortality. The elevated risk for lung cancer was still observable even after adjustment for fine particulate matter.

Keywords

Air Pollution; Epidemiology; Nitrogen Dioxide; Lung Cancer; Mortality

Abbreviations

BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; ICD-10: 10th International Classification of Diseases; LUR: land-use regression; NO_2: Nitrogen dioxide; $PM_{2.5}$: particulate matter with aerodynamic diameter.

1. Introduction

Long-term exposure to air pollution is linked with increased risk of adverse health outcomes. In particular, a number of studies have demonstrated that particulate matter less than 2.5 μm in diameter ($PM_{2.5}$) was associated with all-cause, cardiopulmonary, and lung cancer mortality (World Health Organization 2013).

Nitrogen dioxide (NO_2) is a gaseous air pollutant mainly emitted from traffic-related sources (World Health Organization. 2006). Several reviews examined the association between long-term exposure to NO_2 and mortality (Atkinson et al. 2018; Faustini et al. 2014; Hamra et al. 2015; Hoek et al. 2013), but a recent review noted substantial heterogeneity in the effect estimates between the studies and suggested that the evidence on the association between long-term exposure to NO_2 and mortality is weak (Atkinson et al. 2018). The review pointed out that the heterogeneity depended upon the degree of control for individual confounding factors, such as smoking and body mass index (BMI), and the spatial resolution of the NO_2 concentration estimates. Moreover, a recent report raised concerns about the independent effects of NO_2 in long-term studies because NO_2 and other pollutants have high correlations. Thus, NO_2 may capture the effects of other pollutants (World Health Organization 2013).

Therefore, we examined the association between long-term exposure to NO_2 and all-cause/cause-specific mortality in Japan. To provide a clue for the heterogeneity and the concern raised above, we used a land-use regression (LUR) model to predict the individual-level NO_2 exposure to reduce exposure misclassification and adjusted several important individual potential confounders, such as smoking, BMI, and $PM_{2.5}$.

2. Methods

2.1. Participants

We followed 76,591 participants who underwent health checkups between April 2006 and March 2008 in Okayama City, Japan. Okayama City is an urbanized city with a population exceeding 0.7 million located in the western part of Japan. The health checkups were conducted for residents aged >40 years to check medical conditions. The residents eligible for the basic health checkups were those covered by National Health Insurance, which is one of two types of health insurance system available in Japan, while the other is Employee's Health Insurance (employment-based health insurance). For example, about 50.4% of the residents in Okayama City was eligible for the basic health checkups in the fiscal year of 2006 and about 34.2% of the eligible participants participated the health checkups (Okayama Prefecture 2013). The details of the study setting were described in our previous study (Yorifuji et al. 2019). The participant self-reported medical history (including past medical history and current treatment), lifestyle habits, and physical activity during these basic health checkups. In addition, each participant conducted physical assessment, blood analysis, urinalysis, and electrocardiography in clinics. We followed the subjects until the end of 2016. Because the survival status or cause of death was not available from 22 subjects, we excluded them and left 76,569 subjects for the analysis (Online Figure 1).

2.2. Nitrogen dioxide measurements

We used annual modeled NO_2 data from 2006 and 2007 obtained from the LUR model as the main air pollutant. The LUR models have been developed to model traffic pollutants using existing geographic variables and the LUR models can successfully predict concentrations of individual traffic-related pollutants including NO_2 in the previous epidemiological studies (Kashima et al. 2018). We constructed the models following our previous study (Kashima et al. 2018). We first obtained annual

NO_2 measurement data for Okayama Prefecture in 2006 and 2007 from the Environmental Database managed by the National Institute for Environmental Studies in Japan. Okayama Prefecture is a higher-level administrative region including Okayama City (Figure 1). Using a guideline for effective monitoring stations in Japan (i.e., more than 6000 hours of measurement annually) (Ministry of the Environment in Japan 2010), we obtained annual NO_2 data from 56 stations in 2006 and 57 stations in 2007. We then constructed models that best predicted the monitored levels of annual NO_2 in 2006 and 2007 using geographical variables, such as traffic counts, traffic intensity, land use (buildings, farms, forests, and water areas), and population data. We selected the variables in the LUR models following the ESCAPE protocol (Beelen et al. 2013). The validity of the models were reasonable, i.e., the adjusted R^2 values of the LUR models in 2006 and 2007 were 0.78 and 0.80, respectively.

After constructing appropriate models for each year, we estimated the NO_2 concentrations in each 100 m-square mesh in Okayama City using the selected geographical variables to calculate the annual average NO_2 levels in 2006 and 2007 for each census area. We used census-level information rather than the exact address of each participant for privacy reasons. The census area, approximately corresponding to the area code, is the smallest area used for the National Census, and median of the census area is 0.19 km^2 in Okayama City. We assigned the modeled NO_2 levels in each census area to the participants based on the census area where the participants lived. We then used the average levels of the concentrations in 2006 and 2007 as the main exposure indicator. To exclude participants who were assigned with outlier exposures, possibly because of the modeling, we restricted the participants who were assigned NO_2 concentrations from the first quartile minus 1.5 × interquartile range to the third quartile plus 1.5 × interquartile range (Bland 2015). The NO_2 concentrations are given in ppm in

Japan; thus, we transformed the unit to μg/m^3 by multiplying by 1880 (World Health Organization. 2006).

2.3. Mortality

After identifying the survival status of the participants, we evaluated causes of death for deceased participants by linking records to the vital statistics database of the Ministry of Health, Labour, and Welfare in Japan. As the main outcomes, we focused on all-cause and cause-specific mortality. We coded the causes of death following the 10th International Classification of Diseases (ICD-10): all causes (A00 to R99), cardiopulmonary disease (I10 to 69 and J00 to J99), and lung cancer (C33 to C34). We also targeted specific causes of death from cardiopulmonary disease mortality.

2.4. Statistical analysis

We estimated the hazard ratios (HRs) for a 10-μg/m^3 increase in NO_2 concentrations for all-cause or cause-specific mortality using Cox proportional hazard models. For privacy reasons we could obtain only the month of death or censorship, person-years were thus tallied from April 2006 to the month of death or censorship (e.g., move to other municipalities or the end of the study in December 2016). Because the exact dates when participants undertook the health checkup were not available, we assumed that in April 2006 the participants were already living in the corresponding census area.

We adjusted for age (continuous), sex (dichotomous), and examination year (dichotomous; 2006 or 2007). After that, we adjusted for other confounders including effort to reduce dietary salt intake (dichotomous), effort to reduce intake more vegetables (dichotomous), alcohol consumption (dichotomous; drinker including

regular and occasional drinker or never drinker), smoking (dichotomous; current smoker or not), quantity of smoking (continuous; number of smokes per day), squared quantity of smoking (continuous), years of smoking (continuous), squared years of smoking (continuous), regular exercise (dichotomous; having regular exercise of more than 30 minutes per day for more than one year or not), height (continuous), BMI (categorical; quartile), and total cholesterol (continuous). We defined BMI as body weight (kg) divided by height squared (m^2). We included smoking quantity and square of smoking quantity because a simple linear function does not seem to represent an association between smoking and mortality. We included the height variable to reflect individual socioeconomic status (Honjo et al. 2011; Magnusson et al. 2006; Tyrrell et al. 2016) and total cholesterol because it has been shown to be associated with lower risk of mortality, possibly owing to inflammatory or nutritional processes (Liang et al. 2017). All individual-level variables were obtained at the baseline health checkup and the variables other than examination year, height, body mass index, and total cholesterol were self-reported. As an indicator of area-level socioeconomic status, we finally adjusted for the proportion of white collar workers (such as managerial, professional, technical, or clerical workers) aged over 15 years in the census. We obtained the data from the 2015 National Census. We selected these potential confounders based on the previous epidemiological studies (Beelen et al. 2014; Turner et al. 2017b; Yorifuji et al. 2019).

We also estimated HRs for specific causes of death for cardiopulmonary disease mortality. We also examined the presence of effect modification by stratifying the participants by age (<70 or ≥70 years), sex (male or female), current smoking status (smoker or not), body mass index (above or below the median value of 22.6), current treatment for hypertension, and current treatment for diabetes mellitus; *p*-values for interaction were calculated.

In the sensitivity analysis, we adjusted in the fully adjusted model for annual modeled $PM_{2.5}$ data from 2006 to 2007 obtained from the Atmospheric Composition Analysis Group (van Donkelaar et al. 2016; Yorifuji et al. 2019) to examine the independent effects of NO_2 on all -cause or cause-specific mortality. We adjusted $PM_{2.5}$ because $PM_{2.5}$ is reported to be associated with all-cause, cardiopulmonary, and lung cancer mortality (World Health Organization 2013) and we could obtain individual-level modeled PM2.5 from the Group. The group provided ground-level $PM_{2.5}$ concentration data estimated by combining aerosol optical depth with the GEOS-Chem chemical transport model and calibrated to global ground-based observations of $PM_{2.5}$ using geographically weighted regression. We next used the NO_2 concentration in 2006 as an alternative exposure indicator. We also examined whether the effects of NO_2 were still observable below the WHO guideline for NO_2 (i.e., 40 $\mu g/m^3$). Finally, we examined the association between NO_2 and mortality without excluding the subjects who were assigned with possible outlier NO_2 exposures.

We calculated all confidence intervals (CIs) at the 95% level. Stata SE software (version 16; StataCorp, College Station, TX, USA) was used for all analyses. The study was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences Institutional Review Board (No. 1801-034).

3. Results

The average value of the modeled NO_2 concentrations in 2006 and 2007 in the census areas (with standard deviation) was 31.4 (4.7) $\mu g/m^3$ (Figure 1). NO_2 levels were from 16.2 to 58.9 $\mu g/m^3$. After excluding the subjects who were assigned with possible outlier NO_2 exposures, the NO_2 levels ranged from 19.9 to 41.8 $\mu g/m^3$ and a total of 73,970 participants were included in the analyses (Online Figure 1). The mean age was

70 years and women (67.9%) tended to be enrolled (Table 1). While the participants from the highest NO_2 quartile tended to be women and a smoker, those from the lowest NO_2 quartile were the oldest.

We show the HRs for mortality in Table 2. After adjusting for potential confounders, NO_2 was associated with increased risk of mortality. The HRs were 1.06 (95% CI: 1.02, 1.11) for all-cause mortality, 1.02 (0.96, 1.09) for cardiopulmonary mortality, and 1.36 (1.14, 1.63) for lung cancer mortality following a 10-$\mu g/m^3$ increase in NO_2. The proportional hazard assumption was not violated for the NO_2 exposure using Schoenfeld residuals in any model.

When we examined the association between NO_2 and the specific causes of cardiopulmonary death, NO_2 was not associated with increased risk of cardiopulmonary mortality, but the HR for COPD and related conditions was slightly elevated (Table 3). When we stratified the participants by individual factors, the elderly and smokers tended to have higher effect estimates, and *p*-values for interaction were statistically significant (Online Figure 2).

The correlation coefficient between NO_2 and $PM_{2.5}$ was 0.62. In the multipollutant models with $PM_{2.5}$, although the elevated risks for all-cause and cardiopulmonary mortality were attenuated, NO_2 was still associated with the elevated risk for lung cancer mortality (Table 4). Moreover, when we used the concentration in 2006 as an alternative exposure indicator, the result did not change substantially. The elevated risks were still observable below the WHO guideline. Even when we did not exclude the subjects who were assigned with possible outlier NO_2 exposures, the result did not change substantially.

4. Discussion

We examined the association between long-term exposure to NO_2 as modeled by the LUR model and all-cause and cause-specific mortality in Okayama, Japan. We then found that long-term exposure to NO_2 was associated with increased risk of all-cause and cause-specific mortality after adjusting for potential confounders, but the elevated risks became equivocal after the adjustment of $PM_{2.5}$, except for lung cancer mortality. Moreover, the elevated risks were still observable below the WHO guideline for NO_2.

The long-term exposure to NO_2 estimated by the LUR model increased the risk of mortality even after adjusting for individual-level potential confounders, which could overcome the limitations of the previous studies (Atkinson et al. 2018). Moreover, most of the previous studies were conducted in Europe and North America (Atkinson et al. 2018) and previous studies in Asian countries also suffer from inadequate adjustment of potential confounders and limited special resolution of the exposure assessment (Chen et al. 2016; Dong et al. 2012; Katanoda et al. 2011; Tseng et al. 2015; Zhang et al. 2011). Thus, our study could add further evidence to the previous literature in Asian countries. Adjustment of $PM_{2.5}$, however, attenuated the elevated risk of NO_2 on all-cause mortality. Further evaluation is needed for the independent effects of NO_2.

By contrast, long-term exposure to NO_2 was still associated with elevated risk of lung cancer mortality even after adjustment of $PM_{2.5}$, which is consistent with a previous review (Hamra et al. 2015). Among the cardiopulmonary mortality, NO_2 tended to be more associated with respiratory disease mortality compared to circulatory disease mortality (Table 3), which may also support the harmful effects of NO_2 on lung cancer mortality. NO_2 can initiate a signaling cascade that brings the inflammatory cells into the lung (Kelly 2003) and it can also modulate the cortisol response, which may lead to an impaired anti-inflammatory role of cortisol (Wing et al. 2018). These

mechanisms may explain the harmful effects of NO_2 on respiratory diseases including lung cancer.

Moreover, elderly and smoking participants tended to have higher effect estimates for mortality from natural causes, which may highlight the vulnerability of these populations to air pollution. Although a previous review did not note similar effect modifications (Hoek et al. 2013), some studies demonstrated that smoking and air pollution had greater than additive effects (Turner et al. 2017a; Turner et al. 2014; Yu et al. 2018), consistent with our study. Future studies are warranted to investigate this.

There are several strengths in the present study. First, because we could determine the survival status of most of the subjects and we had information on mobility to other municipalities, the selection bias would be negligible. Second, although previous epidemiological studies relied on the exposure of the between-city contrast, we used the LUR model that can estimate the exposure of the within-city spatial contrast (Nieuwenhuijsen 2015). We thus could estimate individual-level NO_2 exposure of the participants and the validity of the models was reasonable (i.e., the adjusted R^2 values of the LUR models in 2006 and 2007 were 0.78 and 0.80), which could reduce exposure misclassification. Moreover, recent cohort studies have used air pollution data estimated by satellite, but satellite data have low resolution (e.g., 1-km grids) (Jerrett et al. 2017). By contrast, our LUR models had much higher resolution (i.e., 100 -m grids), which could also reduce exposure misclassification. On the other hand, it should be mentioned that because we constructed models that best predicted the monitored levels of annual NO_2 in 2006 and 2007, we could not account for yearly changes in exposure. Third, we could adjust for potential confounders, such as BMI and smoking, obtained from the baseline questionnaire.

By contrast, there are several limitations. First, exposure misclassification is

possible since for privacy reasons we only assigned NO_2 exposure to the census level, but this error would almost be Berkson error causing little or no bias (Armstrong 1998). Second, we utilized the average concentrations from 2006 to 2007 not accounting for yearly changes in NO_2, assuming that the spatial pattern in NO_2 was preserved in the study area. We thus did not have enough data available to evaluate actual long-term exposure to NO_2 in the present study. However, because Okayama City was well-developed and geographically stable, we could assume that the NO_2 spatial pattern did not change substantially in Okayama City. Third, we could obtain follow-up information on a monthly basis. This misclassification would be non-differential because timing of deceased in the months would be independent of air pollution exposure, moving the effect estimates toward the null. Fourth, residual confounding is possible because most of the potential confounders were obtained by self-report. Finally, the eligible participants were covered by National Health Insurance (i.e., publicly-funded healthcare), so they may be older or of lower socioeconomic status than the rest of the population, which may impact the generalizability of the findings.

5. Conclusions

NO_2 long-term exposure was associated with increased the risk of all-cause and lung cancer mortality and the elevated risk for lung cancer was still observable even after adjustment of $PM_{2.5}$ in Japan. Because the harmful effects of NO_2 can be detectable even below the WHO guideline, consideration may be needed to lowering the guideline.

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Figure legend

Figure 1. A map of the study area and nitrogen dioxide exposure distribution