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Short-term exposure to outdoor nitrogen dioxide and respiratory mortality, with high-risk populations: a nationwide time-stratified case-crossover study

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Abstract

Numerous existing studies reported the negative impacts of outdoor nitrogen dioxide (NO_2) on respiratory mortality. However, the evidence of related high-risk populations was considerably limited, especially associated with ages, causes of death, and district-level characteristics. In addition, most earlier studies were based on monitored areas, thus previous risk estimates of NO_2 could be biased to provide nationwide risk estimates and high-risk populations. Therefore, this study performed a nationwide time-stratified case-crossover study to evaluate the association between short-term ambient NO_2 and respiratory mortality in South Korea (2015–2019). A machine learning-ensemble daily NO_2 prediction model was used to cover unmonitored areas. To examine high-risk populations, we assessed NO_2 risk estimates by age group, sex, cause of mortality, and district-level characteristics. In the total population, NO_2 was weakly associated with increased mortality risk due to respiratory disease (OR [odds ratio]: 1.011, 95% CI [confidence interval]: 0.995–1.027), and the association became evident only in individuals aged 80 y or older (1.022, 1.000–1.044), especially related to pneumonia. Further, in people aged 60–69 years, NO_2 was marginally associated with mortality for chronic lower respiratory diseases. Lower district-level socioeconomic status and medical services were marginally related to higher respiratory mortality risks related to NO_2. The excess respiratory mortality fractions and YLL (year of life lost) attributable to NO_2 were 4.13% and 93,851.63 years, and around 70% of the excess deaths were due to noncompliance with the World Health Organization air quality guidelines (daily average $NO_2 > 25$ μg/m^3). This study provides evidence for high-risk populations and the appropriateness of target-specific action plans against NO_2. In addition, based on the excess death estimates, we suggest stricter NO_2 standards are required.

Keywords Nitrogen dioxide, Respiratory mortality, High-risk populations

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Introduction

NO_2 has been known as a common outdoor air pollutant that has hazardous impacts on the respiratory system [22]. NO_2 is involved in the secondary formation of fine particulate matter [31], and it is one of the highly reactive nitrogen oxides (NO_x) from high-temperature combustion processes. Traffic, power plants, and off-road equipment are the major contributors to ambient NO_2 concentrations [10, 17, 37], thus NO_2 concentrations have been considered a proxy of traffic-related air pollutant levels [1].

Historically, multiple human or animal toxicology studies [20] identified that NO_2 is a major risk factor for dysfunctions in the respiratory system including respiratory infections, [11], asthma [1], and decreasing pulmonary function [40]. Existing in vitro and experimental studies revealed that exposure to NO_2 increases oxidative stress, inflammatory response to inhaled allergen in bronchi, and the reactive oxygen and nitrogen species [3, 4]. NO_2 inhalation also can lead to lung malfunctions, accelerate pulmonary infections, and degenerate lung diseases through a pro-inflammatory response (which is an automatic immune response) [20].

Furthermore, the association between outdoor NO_2 and respiratory mortality is less understood, compared to particulate matter and ozone [37]. First, because many previous studies have investigated the association between NO_2 and all-cause or non-accidental mortality [31, 32], epidemiological evidence for the NO_2 risk of respiratory mortality with more specific causes of death was limited, despite plausible biological mechanisms we mentioned earlier, such as oxidative stress, inflammatory response, and increased pulmonary infections. Second, since monitoring stations were generally operated in metropolitan urban areas or industrial areas, many relevant studies have investigated well-monitored areas [31, 32]. This point suggests that previous NO_2 risk estimates might be biased due to limited information on less-monitored [16]. Third, to our knowledge, few studies have examined spatial differences in NO_2-related respiratory mortality risks depending on regional characteristics with large data [37], although examining regional differences could be important for effective and righteous public health resource allocation and mobilization. Lastly, studies on the excess mortality burden attributable to NO_2 were limited.

To address these gaps in knowledge, we performed a nationwide time-stratified case-crossover study, with the national respiratory mortality records and a machine learning-based NO_2 prediction model from 2015 through 2019 in South Korea. To reveal detailed high-risk populations, this study examined the heterogeneous associations between NO_2 and respiratory mortality by age group, cause of death, sex, and district-level characteristics. Further, we estimated the excess mortality burdens due to the entire NO_2 and due to NO_2 concentrations above the 2021 World Health Organization (WHO) air quality guidelines (daily average $NO_2 > 25$ μg/m^3).

Methodology

Study populations

This study included all people residing in South Korea who died of respiratory disease and were registered in Statistics Korea. We obtained individual-level respiratory mortality data covering all 247 districts of inland South Korea (except Jeju and Ulleung islands) from 2015 to 2019. The International Classification of Disease 10th Revision (ICD-10) was used to define respiratory death in our study (ICD-10: J00–J99).

However, due to the identification problem, Statistics Korea only provides the causes of respiratory death based on the three-character "category of the diagnosis" of ICD-10. Thus, we could collect three specific causes of respiratory death: pneumonia (J12–J18), chronic lower respiratory diseases [CLR] (J40–J47), and other respiratory diseases (respiratory diseases that were not classified into the above three specific diseases). We were unable to analyze the mortality for influenza separately because of the small sample size (less than 3,000 cases, annually). Thus, we classified influenza into the "other respiratory disease" category.

Further, to examine the different associations between NO_2 and mortality by age, we classified ages at death into five categories: total (all ages), individuals aged 0–59 y, 60–69 y, 70–79 y, and those aged 80 or older.

Study design

This study adopted a time-stratified case-crossover design to estimate the association between NO_2 and respiratory mortality. This approach has been recognized as a standardized method to estimate the association between short-term exposure to air pollution and health outcomes [21, 25] by controlling for time-invariant (or less variant) confounders and time trends. Detailed explanations of the study design are in the Supplementary Materials ("1. Study design").

Air pollution and environmental data

We collected nationwide district-level modeled NO_2 (ppm) and $PM_{2.5}$ (μg/m^3) from machine-learning ensemble prediction models from 2015 to 2019 (study years). These models were developed by the AiMS-CREATE team and their models were used in previous published studies [24, 33]. More detailed information on the ensemble prediction model is provided in the Supplemental Materials, "2. Air pollution prediction models". The

prediction models for daily NO_2 and $PM_{2.5}$ showed good performances during the study period: cross-validated R^2 values of 0.95 and 0.94 (Table S1). Although previous studies used a relatively short lag period of NO_2 (e.g., lag 0–1) as the main exposure [6, 12, 15, 31], several studies reported that the impacts of air pollution on respiratory outcome could have longer lag days; some existing studies suggested the plausible mechanisms that exacerbation of respiratory infections would be expected to take more time [38, 39] and complex interactions between air pollutants and antioxidants in the lung lining fluid compartment could contribute to the delayed deterioration of respiratory reactions [34]. Therefore, we tried to find an optimal moving average period of NO_2 (up to a week) based on the lowest Akaike Information Criterion (AIC). As a result, the average NO2 from the same day to five lag days (lag 0–5) was selected as the main exposure.

We also collected district-level 2 m air temperature (K), relative humidity (%), and precipitation (m) from the ERA-5 Land global reanalysis dataset [7]. This ERA-5 dataset has a horizontal resolution of $0.1^\circ \times 0.1^\circ$, thus we assigned it to each district by averaging the values at grid cells with centroid points inside the boundary of each district [35].

District indicators

To examine the effect modifications by district-level characteristics, we obtained data on six indicators covering urbanicity, accessibility to parks, health behaviors, and socioeconomic levels. Detailed information on data sources and explanations of the selected district indicators is in the Supplementary Materials ("3. District-level indicators"). Briefly, we first collected population density (persons per km^2) to address different urbanicity [26]. Second, to examine the urban green spaces [8, 19], the accessibility to parks in the living sphere (hereafter, park accessibility; distance to neighboring parks from each grid) was collected. Third, we obtained two variables related to regional health behaviors: the proportions of current smoking and obesity [23]. To examine the effect modification by regional socioeconomic status, we collected the proportion of people who received the National Basic Livelihood Security and the proportion of people who could not visit the medical facilities when they wanted within a year [23]. We classified each indicator into three categories (high, middle, and low) based on their tertiles for the statistical analysis [8].

Statistical analysis

We created a time-stratified case-crossover dataset for each age group, cause of death, and sex (a total of 40 combinations in the main analysis: five age categories, sexes, and four respiratory deaths). For each case day (i.e., date of death), we set matched control days as days with the same day of the week and month within the same year. This time-stratified self-matching controls the confounding from time-invariant variables or variables that do not change substantially in a month, such as body mass index, and diet [45]. Further, the bidirectional time-stratified matching also controlled for potential confounding for the day of the week, seasonality, and long-term trends of NO_2 and outcomes [28]. We performed a conditional logistic regression to evaluate the associations between short-term exposure to NO_2 and respiratory mortality in each case-crossover dataset.

As the main analysis, we performed NO_2 single pollutant models. To control for potential confounding, we adjusted for relative humidity, precipitation (as linear terms with lag 0–1), and temperatures (lag 0–3) with a natural cubic spline with six degrees of freedom based on previous large studies on air pollution and mortality [6, 29, 31]; however, it was also based on our grid search for optimal modeling specifications based on the lowest Akaike Information Criterion. We measured the association between short-term NO_2 and respiratory mortality with odd ratios (ORs) for a 0.01 ppm (10 ppb) increase in lag 0–5 NO_2. In addition, to check the potential nonlinear relationship between NO_2 (0–5) and respiratory mortality, we conducted a conditional logistic regression with a natural cubic spline (including equally spaced three internal knots for NO_2), instead of the linear term of NO_2 in the main model.

To find high-risk districts, we performed analyses to examine which district-level characteristics modify the association between NO_2 and respiratory mortality. For each case-crossover dataset divided by causes of death, we added an interaction term between NO_2 and categorized district indicators (tertiles) and repeated the main analysis. The time-stratified self-matching design already controlled the potential confounding from district-level characteristics that did not change within a month, thus the interaction was included in a conditional logistic model individually for each indicator.

We performed sensitivity analyses to examine the consistency of our results in relation to different modeling specifications and two pollutant models ($PM_{2.5}$ adjusted). Across all statistical analyses, R software (version 4.2.1) with package "*survival*" was used.

Excess respiratory mortality and Years of life lost from mortality attributable to NO_2

To assess the excess respiratory mortality burden due to short-term exposure to NO_2, we translated our estimated ORs into excess deaths and YLL (years of life lost from mortality) attributable to NO_2. Detailed processes for the excess respiratory mortality burden estimation are in the

Supplementary Materials ("4. Estimation of the excess respiratory mortality burden attributable to short-term exposure to ambient NO_2"). Briefly, we first allocated the individual YLLs based on the national life expectancy estimation in 2019 (Statistics Korea 2024). Based on the estimated ORs from the main analysis, we calculated daily and total excess deaths and YLL, and the total excess deaths ratio with the total number of respiratory deaths provide the total excess fraction (%) of respiratory deaths attributable to short-term NO_2 exposures. Further, to assess the excess mortality burden due to non-compliance with the current 2021 WHO guidelines, we calculated excess respiratory deaths and YLL only for the subset of days with NO_2 levels above (i.e. non-compliance) the WHO air quality guidelines (daily average $NO_2 > 25\ \mu g/m^3$).

Results

Table 1 shows descriptive statistics of respiratory mortality during the study period. During the study period, a total of 161,059 mortality cases were included in this study. Among causes of respiratory death, pneumonia, CLR, and other respiratory diseases showed 95,201 (59.1%), 33,478 (20.8%), and 32,380 (20.1%) cases, individually. Percentages for the causes of respiratory death were calculated as a proportion of the total number of respiratory disease cases. Individuals aged 80 y or older showed the largest mortality counts for (total) respiratory disease (103,271; 55.7%) and males showed higher counts (89,687) than females (71,371). Figure 1 presents the average geographical distribution of average NO_2 (left) during the study period (0.012 ppm on average) and total respiratory death counts (right).

Figure 2 exhibits a nonlinear association between NO_2 and respiratory mortalities. Except for mortality due to other respiratory diseases, mortality due to respiratory diseases had an approximately linear association with short-term exposure to NO_2. Mortality due to other respiratory diseases also showed a positively linear association with NO_2 after around 0.015 ppm.

Figure 3 presents the cause-specific associations between NO_2 and respiratory mortality in the total age and by age group. In the total age, the associations between NO_2 and respiratory mortality were observed, with an OR of 1.022 with 95% CIs: 1.004–1.040. The association with respiratory disease was not evident in people aged less than 80 y, and those aged 80 y or older only showed an association with NO_2: OR: 1.034 (95% CI: 1.012–1.057). Other respiratory disease deaths (pneumonia, CLR, and other respiratory diseases) also showed the similar age pattern: individuals aged 80 y or older showed the highest ORs. Figure S1 displays the age-specific association between NO_2 and respiratory mortality by sex.

Table 1 Descriptive statistics on respiratory mortality data the study used (2015–2019)

Causes of death	Age categories	Case	%
Respiratory disease	**Total**	161,059	100.0
	0–59 y	6,396	4.0
	60–69 y	11,741	7.3
	70–79 y	39,628	24.6
	80 y and older	103,271	64.1
	Females	71,372	44.3
	Males	89,687	55.7
Pneumonia	**Total**	95,201	59.1
	0–59 y	3,709	2.3
	60–69 y	5,847	3.6
	70–79 y	21,100	13.1
	80 y and older	64,531	40.1
	Females	45,529	28.3
	Males	49,672	30.8
Chronic lower respiratory diseases	**Total**	33,478	20.8
	0–59 y	884	0.5
	60–69 y	2580	1.6
	70–79 y	8964	5.6
	80 y and older	21,043	13.1
	Females	12,248	7.6
	Males	21,230	13.2
Other respiratory diseases	**Total**	32,380	20.1
	0–59 y	1803	1.1
	60–69 y	3314	2.1
	70–79 y	9564	5.9
	80 y and older	17,697	11.0
	Females	13,595	8.4
	Males	18,785	11.7

Based on the point estimates, we could not observe risk differences between females and males.

Figure 4 shows the associations between NO_2 and respiratory death depending on district indicator categories in the total population. *P*-values in Fig. 3 indicate the statistical test results on the effect modification (i.e. differences in ORs for middle or high levels compared to OR for low levels). We could not find statistically evident effect modifications by district characteristic for the total respiratory deaths. While the association between NO_2 and pneumonia death was lower in high density areas than in low density areas (P-value: 0.060). Except for it, we could not find a consistent effect modification.

Figure 5 displays the effect modifications by district-level indications in the associations between NO_2 and respiratory death depending on two age groups (individuals aged 50–59 y and aged 80 or older). We could not find a consistent effect modification pattern between the two age groups. The marginal effect modification of the

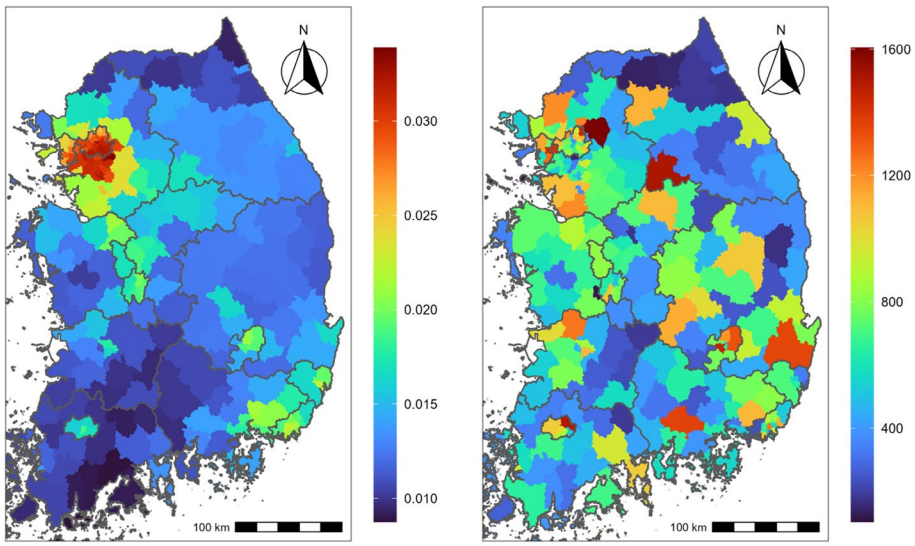


Fig. 1 Geographical distributions of the district-level averages of daily average NO_2 (ppm [left]) and total death counts [right] in South Korea from 2015 through 2019. NO_2: nitrogen dioxide

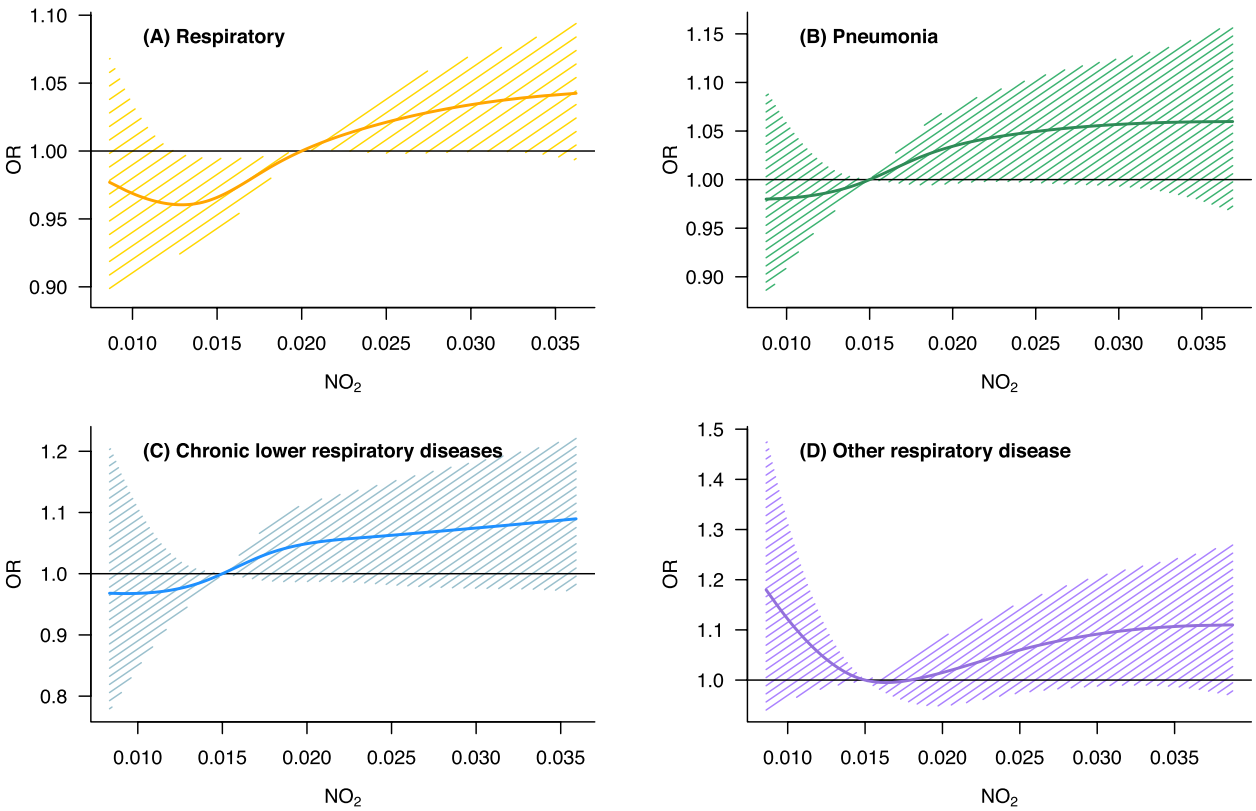


Fig. 2 Nonlinear associations between exposure to NO_2 (lag 0–5) and respiratory mortalities. **A** total respiratory deaths, **B** Deaths due to pneumonia, **C** Deaths due to chronic lower respiratory diseases, **D** Deaths due to other respiratory diseases (not classified into pneumonia or chronic lower respiratory-related deaths). NO_2: Nitrogen dioxide (ppm)

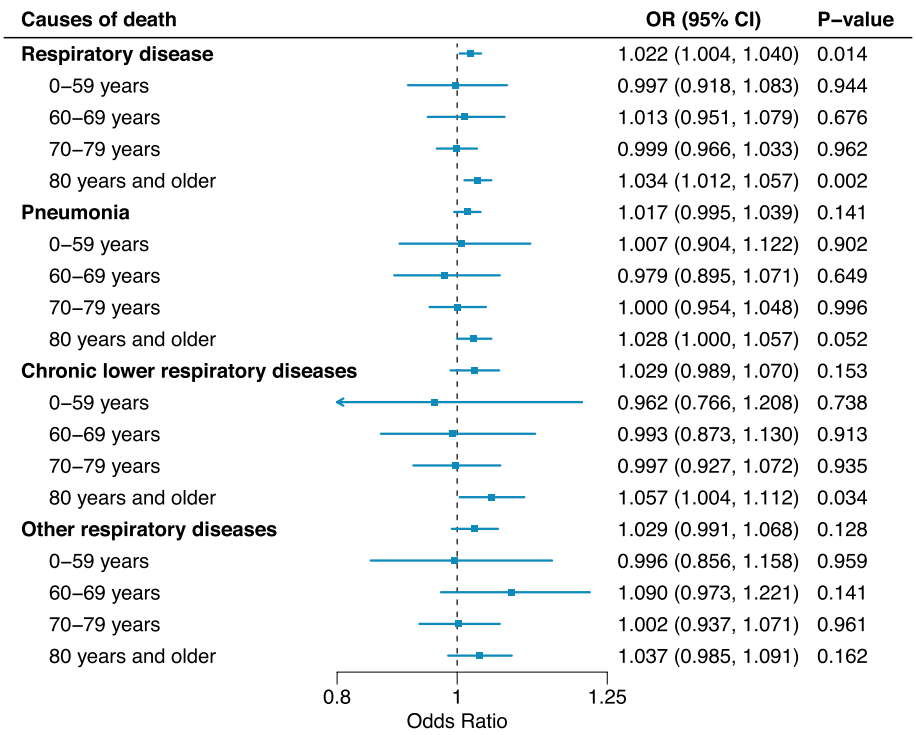


Fig. 3 Associations between short-term NO_2 exposure (lag 0–5) and respiratory mortality by age group and cause of respiratory mortality. NO_2: nitrogen dioxide. Odd ratios (ORs) for a 0.01 ppm (10 ppb) increase in NO_2

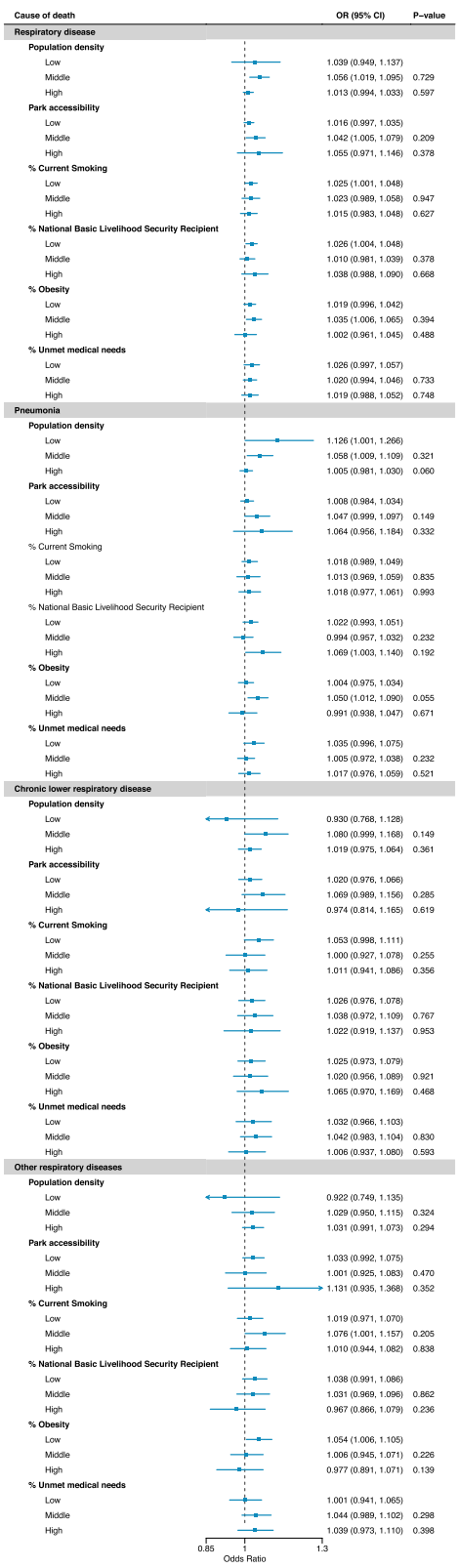
proportion of National Basic Livelihood Security Recipient was observed only in individuals aged 80 or older, especially related to pneumonia and CLR deaths. The corresponding results to Fig. 4 for people aged 60–69 y and 70–79 y are exhibited in Figure S2, and we could not observe evident differences between the two age groups. In addition, although we could not find pronounced differences in effect modification patterns between sexes, the effect modifications by the proportion of Unmet medical needs were marginally more prominent in females than in males based on the point estimates (Figure S3).

Table 2 displays the estimated excess mortality and YLL attributable to short-term NO_2 exposures by cause of death. For respiratory mortality, the excess mortality fraction attributable to NO_2 was 4.13 (95% CI: 0.87–7.40). Based on the point estimates, the excess fraction was higher in CLR mortality (5.29%) than pneumonia mortality in the total age. Further, the excess respiratory mortality fraction attributable to NO_2 due to noncompliance with WHO air quality guidelines was 3.06%, and it accounted for over 60% of the total excess respiratory mortality attributable to NO_2. Table S2 reports the excess mortality numbers attributable to NO_2; the absolute number of excess deaths was the highest in pneumonia deaths due to the large numbers of pneumonia deaths. Table 2 also shows the excess YLL attributable to NO_2, and the excess YLL was 93,851.63 years (95% CI: 19,779.11 years–167,983.69 years) for respiratory mortality in the total population, and it was the highest for pneumonia death (42,261.11 years, −13,775.96.24 years–97,815.11 years) compared to other causes of respiratory death.

Lastly, in the sensitivity analyses (Table S3), we could observe that our risk estimates in the total and by age groups were generally less affected by different modeling specifications.

Discussion

This study assessed the nationwide association between short-term exposure to NO_2 and respiratory mortality in South Korea from 2015 through 2019. To our knowledge, this is the first and largest nationwide study addressing the association between NO_2 and respiratory mortality as well as the excess respiratory mortality burden due to NO_2 in South Korea. We found that the association between NO_2 and respiratory disease was the strongest in people aged 80 y or older compared to other age groups, especially for pneumonia death. Although the statistical evidence was weak, we found marginal effect modifications by certain district-level characteristics. Particularly, a higher proportion of National Nasic Liveliuhood



◀ **Fig. 4** Effect modifications by district-level indicators in the NO_2 (lag 0–5)-respiratory mortality risk in the total population. *P*-values indicate the statistical test results on the effect modification (i.e. magnitude of differences in estimates for middle or high-levels compared to low-level; not for the hypothesis that OR is one). %: proportion. NO_2: nitrogen dioxide. Odd ratios (ORs) for a 0.01 ppm (10 ppb) increase in NO_2

Security Recipient was marginally associated with higher NO_2-respiratory mortality risk, and the association was slightly more evident in people aged 80 y or older than other age groups. Lastly, we estimated the excess respiratory mortality burden attributable to short-term NO_2 and found that over 60% of the excess burden attributable to NO_2 was related to non-compliance with the current WHO air quality guidelines.

Our findings are generally consistent with previous studies. A multi-country study with a large dataset including 5.5 million mortality cases showed that short-term NO_2 was associated with increased respiratory mortality risk [31]. One European multi-city study also revealed the short-term impact of NO_2 on increased respiratory mortality [38]. A systemic review study including 87 research articles from multiple continents reported that short-term NO_2 and mortality reported that a 0.01 ppm increase in NO_2 was associated with a 2.05% increase in respiratory mortality [43]. Our study estimated around a 1.1% increase in respiratory mortality per 0.01 ppm increase in NO_2. However, it should be carefully interpreted because study periods and regions were heterogeneous between our study and the review study.

One of the novel findings of this study was examining the different associations between NO_2 and respiratory mortality by age group and the cause of respiratory death. We found that total respiratory mortality risk estimates related to NO_2 were the highest in people aged 80 or older, and the association was not generally observed in people less than 80 y. Whereas previous studies reported that the short-term NO_2 risks for respiratory disease-related mortalities became more evident in people aged around 65 y [9, 38, 42], which is much lower than our high-risk age. These discrepancies should be interpreted carefully because the traditional concept of "the elderly" might have changed in recent years. Due to the rapid advances in medicine and science, the overall health of people has consistently improved during recent decades, globally [14]. Although the evidence of this study is highly limited, we conjecture that the differences between previous studies and our findings regarding age group might be related to the research period of

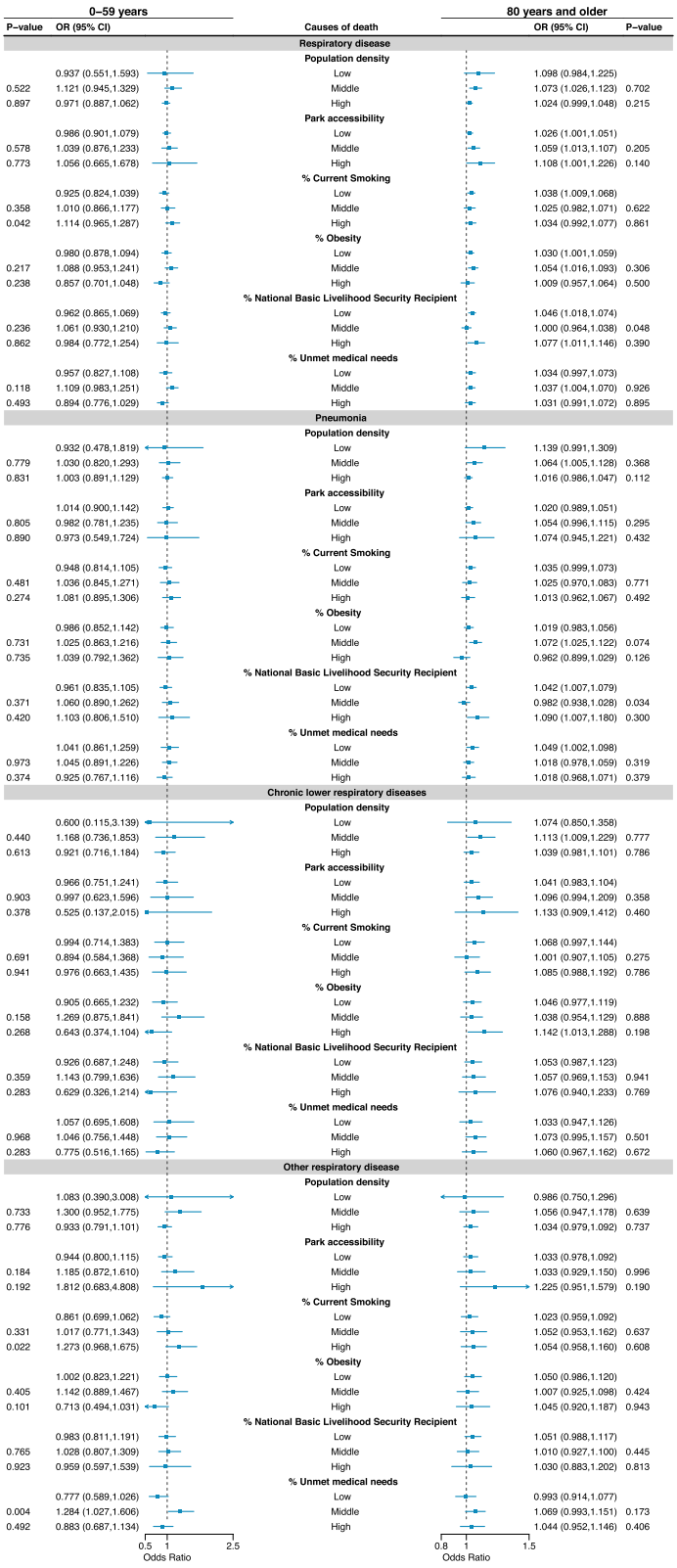


Fig. 5 Effect modifications by district-level indicators in the NO_2 (lag 0–5)-respiratory mortality risk in the individuals aged 0–59 y and aged 80 y or older. *P*-values indicate the statistical test results on the effect modification (i.e. magnitude of differences in estimates for middle or high-levels compared to low-level; not for the hypothesis that OR is one). %: proportion. NO_2: nitrogen dioxide. Odd ratios (ORs) for a 0.01 ppm (10 ppb) increase in NO_2

Table 2 Excess death fractions and YLL (Year of Life Lost from mortality) attributable to ambient short-term exposure to NO_2 (lag 0–5) for respiratory mortalities. NO_2: nitrogen dioxide

Cause of death		All-range of $PM_{2.5}$		WHO guideline compliance	
	Age group	Excess deaths (%)	Excess YLL (years)	Excess deaths (%)	Excess YLL (years)
Respiratory disease	**Total**	4.13 (0.87–7.4)	93,851.63 (19,779.11–167,983.69)	3.06 (0.65–5.44)	70,137.1 (14,924.97–124,721.11)
	0–59 years	−0.86 (−18.39–14.72)	−19,527.33 (−418,028.33–334,285.78)	−0.77 (−14.43–10.63)	−17,708.82 (−330,805.7–243,721.42)
	60–69 years	2.44 (−10.09–14.01)	55,505.05 (−229,293.12–317,974.14)	1.75 (−7.76–10.13)	40,197.35 (−177,779.19–232,242.61)
	70–79 years	−0.18 (−7.12–6.56)	−4045.92 (−161,835.04–148961.15)	−0.16 (−5.43–4.84)	−3555.95 (−124,559.71–110,827.91)
	80 y and older	6.38 (2.36–10.37)	144,936.7 (53,639.82–235,570.93)	4.7 (1.76–7.57)	107,715.31 (40,326.26–173,614.0)
Pneumonia	**Total**	3.25 (−1.06–7.51)	42,261.11 (−13,775.96–97,815.11)	2.4 (−0.79–5.51)	31,446.79 (−10,397.91–72,265.19)
	0–59 years	0.8 (−22.4–20.45)	10,366.55 (−291,683.25–266,162.39)	0.38 (−17.72–14.53)	5001.6 (−232,121.31–190,382.81)
	60–69 years	−4.6 (−24.91–13.15)	−59,917.22 (−324,379.29–171,133.55)	−3.65 (−19.83–9.51)	−47,859.08 (−259,737.78–124,663.67)
	70–79 years	−0.08 (−9.78–9.1)	−1081.76 (,318.91–118,431.39)	−0.1 (−7.5–6.65)	−1355.59 (−98,207.76–87,150.48)
	80 y and older	5.16 (0.01–10.22)	67,144.59 (127.83–133,002.25)	3.8 (0.01–7.45)	49,743.69 (96.23–97,599.13)
Chronic lower respiratory diseases	**Total**	5.29 (−1.99–12.31)	24,599.6 (−9280.38–57,233.47)	3.74 (−1.45–8.61)	17,634.43 (−6812.12–40,567.73)
	0–59 years	−10.83 (−71.44–30.64)	−50,521.6 (−333,313.62–142,297.7)	−9.22 (−61.22–20.51)	−43,598.38 (−289,370.71–96,513.75)
	60–69 years	−2.17 (−30.78–21.26)	−10,150.65 (−143,404.53–98,794.91)	−1.88 (−23.93–14.56)	−8872.69 (−112,947.0–68525.47)
	70–79 years	−0.77 (−15.82–12.87)	−3606.25 (−73,670.91–59,853.0)	−0.65 (−11.86–8.99)	−3066.53 (−55,941.99–42,366.33)
	80 y and older	9.89 (0.87–18.41)	45,973.81 (4030.89–85,569.0)	6.93 (0.62–12.69)	32,627.65 (2938.14–59,761.22)
Other respiratory diseases	**Total**	5.59 (−1.63–12.55)	28,089.73 (−8171.77–63,042.9)	4.28 (−1.28–9.5)	21,697.38 (−6459.24–48,134.97)
	0–59 years	−2.04(−37.99–25.92)	−10,262.43 (−191,068.05–130197.1)	−2.1 (−32.56–18.99)	−10,590.46 (−164,773.03–96204.4)
	60–69 years	15.27(−5.76–32.91)	76,697.6 (−28,953.94–165,229.39)	11.31 (−4.56–23.69)	57,318.75 (−23,117.37–120,027.21)
	70–79 years	0.16(−14.33–13.35)	801.43 (−72,059.09–67063.9)	0.03 (−11.6–10.09)	172.12 (−58,739.01–51104.78)
	80 y and older	6.92(−2.89–16.15)	34,780.85 (−14,535.22–81,143.28)	5.27 (−2.28–12.12)	26,711.78 (−11,524.58–61,410.34)

each study. The three studies we mentioned above have been performed from 1990–1997 in 30 European cities [38], 1997–2007 in Santiago [9], and 1998–2001 in Hong Kong [42]. However, a recent multi-country study involving Jiangsu (China), California (the United States), Central-southern Italy, and Germany from 2015–2019 reported no NO_2 risk on mortality or substantially small risk estimates in people aged less than 75 y, and the association between NO_2 and mortality became more pronounced after 75 y in all countries [30]. These results are generally consistent with our findings with the same study period: 2015–2019. Of course, although it should be interpreted with extreme caution because there might be a lot of potential confounders, we cautiously suggest that the concepts of high-risk populations regarding "the elderly" might need to be re-discussed in-depth from the perspective of health risks related to air pollution.

In addition, we found that the association between NO_2 and mortality for other respiratory disease was more pronounced in people aged 60–69, although the

statistical evidence was insufficient. According to the ICD-10 category, the other respiratory disease mortality we used included mortality for influenza, acute respiratory infections, etc. Previous animal and human studies have identified that NO_2 inhalation negatively affects these diseases [5, 47]. Although this study is limited in providing exact evidence, previous studies might suggest some hypotheses: existing studies revealed that individuals with early COPD were related to an increased risk of acute respiratory hospitalization and early death [13, 44]. In addition, based on the Korean National Health and Nutrition Examination Survey in 2018 [23], the current smoking rate was much higher in individuals aged 60–69 (14.9%) than in individuals aged 70 y or older (6.6%). Thus, we cautiously surmised that relatively young elderly with risk factors for severe acute respiratory diseases, like influenza, could be more vulnerable to respiratory mortality risks related to NO_2 compared to other older age groups because of poorer pulmonary health conditions and health behaviors, although more studies are required.

Our findings related to effect modification by district-level characteristics also should be interpreted carefully. Although the statistical evidence was relatively weak, we found areas with low population density showed a higher NO_2-related respiratory mortality risk in total respiratory and pneumonia deaths. Along with a high average age of people living in low-density areas (i.e., rural areas) [23], we conjecture that poorer accessibility to medical facilities in low-density areas could be associated with a higher vulnerability to environmental stressors, which was addressed in a previous study [26]. Further, although the finding was also statistically weak, we observed that areas with the highest proportion of Basic Livelihood Security Recipient needs generally exhibited the highest NO_2-respiratory mortality risk, based on the point estimates. However, although the statistical evidence was substantially weak, areas with a low proportion of Unmet medical needs generally showed a higher NO_2-respiratory mortality risk compared to areas with a high proportion of Unmet medical needs, especially for pneumonia death. Although this study could provide limited evidence, we carefully conjecture that there might be an ecological bias. In South Korea, the proportion of Unmet medical needs was generally lower in urban cities, although some metropolitan areas (Ulsan and Incheon metropolitan cities) and more urbanized regions (Gyeonggi and Gyeongnam provinces) had a higher proportion of Unmet medical needs [23] due to their large population size. In other words, the reason for the higher NO_2-related respiratory death in areas with a low proportion of Unmet medical needs might be confounded by the urbanicity level; however, further studies are required. In addition, we found that the proportion of National Basic Livelihood Security Recipients modified the NO_2-respiratory mortality risk in individuals aged 80 or older, especially related to pneumonia death [23]. Several studies have reported that lower socioeconomic status and poorer health behaviors are closely linked to a higher risk of severe respiratory diseases [2, 27, 36]. Thus, although ecological bias from the district-level data could be considered, our findings could suggest that improving community-level socioeconomic status can mitigate respiratory deaths related to NO_2, especially in "older seniors" (aged 80 y or older) who likely have lower immunity than other younger groups [46].

In addition, our results on the excess respiratory deaths and YLL attributable to short-term NO_2 provide important implications for public health and environmental policies. We found that the excess respiratory mortality fraction attributable to NO_2 related to non-compliance with the current WHO air quality guidelines (daily average $NO_2 > 25$ μg/m^3) accounted for over 60% of the total excess mortality due to NO_2. It indicates the necessity and social benefits of stricter air quality standards regarding NO_2 in South Korea, especially, given the current air quality guidelines of South Korea (0.06 ppm [~ 110 μg/m^3] for 24-h average NO_2) that are much higher than the WHO guidelines.

Several limitations should be acknowledged. First, we adopted a time-stratified case-crossover design to control confounders that did not substantially change within a month. However, unmeasured short-term time-dependent confounders, such as daily high-risk activities and smoking, etc., might affect our risk estimates. Second, because the national mortality data of this study provided only district-level residential addresses at death (the median size of districts in South Korea: 397 km^2, which is around 1.7 times larger than the median size of the US zip code areas), thus exposure misclassification could exist. Third, we could not address more specific respiratory diseases, because of the limited data availability. In particular, we were limited in addressing more detailed causes of respiratory death, like asthma, influenza, and COPD, which could be acute, severe, and related to NO_2. Lastly, due to the insufficient sample size of each specific category, our risk estimates regarding subgroups were statistically weak in general, except estimates for those aged 80 y or older. Many previous epidemiological journals did not recommend using the P-value of the criteria of the significance [18] because the P-value depends on the sample size and most epidemiological studies were based on observational studies without planned samples to test the primary hypothesis. However, because the P-value and 95% confidence interval could provide evidence for the reliability of the association and possibilities of sampling and information errors, our results

should be carefully interpreted when the corresponding statistical evidence is weak. In addition, our results for the total population and people aged 80 years or older (with strong statistical evidence) could provide more reliable evidence on the association between NO_2 and respiratory mortality, along with high-risk populations.

Nonetheless, this study has several strengths. First, with high-accuracy machine learning exposure modeling, this study assessed the nationwide association between short-term exposure to outdoor NO_2 and respiratory mortality in South Korea. Second, by stratified and interaction analyses, we examined the heterogeneous association between NO_2 and respiratory mortality by age group, cause of death, sex, and regional characteristics and suggested specific high-risk populations. Our findings provide important evidence for more targeted action plans to reduce the health impacts of NO_2. Third, by estimating the excess mortality burden attributable to non-compliance with the WHO air quality guidelines, this study suggests the social benefits and justification for establishing more stringent NO_2 air quality standards.

Conclusion

In summary, we assessed the nationwide association between short-term ambient NO_2 and respiratory mortality in South Korea and provided evidence regarding high-risk populations. This study also provides findings that might indicate the latent benefits of stricter NO_2 air quality guidelines and potential effect modifications by individual and community-level characteristics that could provide partial evidence for more effective public health resource mobilization.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-21048-w.

Supplementary Material 1.

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Authors' contributions
Contributions Seoyeong Ahn: Formal analysis, Data curation, Visualization, Writing – Original draft Hyewon Yun: Formal analysis, Data curation, Visualization, Writing – Original draft Sooyoung Kim: Formal analysis, Data curation, Visualization Yejin Kim: Data curation, Writing – Original draft Jieun Oh, Hyemin Jang: Data curation, Writing – review & editing Sojin Ahn: Writing – review & editing Cinoo Kang, Ayoung Kim, Dohoon Kwon, Jinah Park, Insung Song, Jeongmin Moon, Jieun Min, Ejin Kim: Data curation Ho Kim: Writing – review & editing, Funding acquisition. Whanhee Lee: Conceptualization, Methodology, Investigation, Supervision, Writing – Original draft, Funding acquisition.

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Data availability
The data of this study can be provided upon request to the corresponding authors.

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board (IRB) of Pusan National University (Review Exemption; IRB number: 2024_196_HR). The IRB approval process also waived the requirement for informed patient participation consent because this study used secondary and publicly available data (https://mdis.kostat.go.kr/index.do). The data of this study did not include any information related to personal identification.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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