Nitrogen dioxide increases the risk of mortality in idiopathic pulmonary fibrosis

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Exposure to nitrogen dioxide is associated with increased risk of mortality in patients with idiopathic pulmonary fibrosis, particularly in elderly males https://bit.ly/35dopLn

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ABSTRACT Ambient air pollution is associated with the prognosis of idiopathic pulmonary fibrosis (IPF) patients. We aimed to identify the impacts of individual exposure to particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) and nitrogen dioxide (NO_2) on IPF patients' mortality.

1114 patients (mean age 65.7 years; male 80.5%) diagnosed with IPF between 1995 and 2016 were included in this study. Individual-level long-term concentrations of PM_{10} and NO_2 at residential addresses of patients were estimated using a national-scale exposure prediction model. The effect of PM_{10} and NO_2 on mortality was estimated using a Cox proportional hazards model adjusted for individual- and area-level covariates.

The median follow-up period was 3.8 years and 69.5% of the patients died or underwent lung transplantation. When adjusted for individual- and area-level covariates, a 10 ppb increase in NO_2 concentration was associated with a 17% increase in mortality (hazard ratio (HR) 1.172, 95% CI 1.030–1.344; p=0.016). When IPF patients were stratified by age (⩾65 *versus* <65 years) or by sex, NO_2 was a significant prognostic factor for mortality in the elderly (HR 1.331, 95% CI 1.010–1.598; p=0.010). When stratified by age and sex jointly, NO_2 showed the stronger association with mortality in elderly males (HR 1.305, 95% CI 1.072–1.598; p=0.008) than in other groups. PM_{10} was not associated with IPF mortality in all patients and in subgroups stratified by age or sex.

Our findings suggest that increased exposure to NO_2 can increase the risk of mortality in patients with IPF, specifically in elderly males.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial pneumonia of unknown aetiology with poor prognosis [1–3]. Various prognostic factors of mortality in patients with IPF include older age [4], smoking status [5], lower body mass index (BMI) [6], lower lung function [5], more extensive fibrosis on chest computed tomography [7] and presence of pulmonary hypertension [8]. Moreover, some studies suggested an association between air pollution and clinical course of IPF [9–13]. An Italian study found an association between IPF incidence and nitrogen dioxide (NO_2) concentration during the cold season in Northern Italy [11]. In a study using a Korean IPF cohort (n=436), exposure to NO_2 (hazard ratio (HR) 1.41, 95% CI 1.04–1.91; p=0.03) and ozone (HR 1.57, 95% CI 1.09–2.24; p=0.01) over the previous 6 weeks was associated with the occurrence of acute exacerbation when adjusted for smoking status and forced vital capacity (FVC) [9]. In another study using a French IPF cohort (n=192), cumulative exposure to particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}) (HR 2.01, 95% CI 1.07–3.77, per 10 $\mu g \cdot m^{-3}$; p=0.03) and ⩽2.5 µm ($PM_{2.5}$) (HR 7.93, 95% CI 2.93–21.33, per 10 $\mu g \cdot m^{-3}$; p<0.001) was positively associated with mortality in patients with IPF when adjusted for age, smoking status, FVC and diffusing capacity of the lung for carbon monoxide (D_{LCO}) [10]. However, these findings were based on the air pollution concentrations measured at limited numbers of air quality regulatory monitoring sites, mostly distant from patients' homes.

The exposure misclassification derived from using limited monitoring data can lead to inaccurate effect estimates in subsequent health effect analysis. The impact of the discrepancy could even be greater when the limited number of regulatory monitoring sites is applied to represent air pollution exposure of hundreds to thousands of study participants, as often found in previous studies [9–11]. Considering the characteristics of patients with IPF, who are mostly elderly adults with poor performance status due to dyspnoea, estimation of individual air pollution concentrations based on patients' home addresses can help elucidate the association with their health end-points. Therefore, our study aimed to estimate long-term exposure to NO_2 and PM_{10} at residential addresses using a previously validated air pollution prediction model and to assess the impact of exposure on mortality in patients with IPF.

Materials and methods

Study population

1144 patients (biopsy-proven cases 33.6%) were diagnosed with IPF between July 1995 and January 2016 at the Asan Medical Center (Seoul, Republic of Korea) and screened for this study. After excluding subjects whose baseline pulmonary function data (n=28) or survival status (n=2) was not available, 1114 patients were finally included. All of the patients met the diagnostic criteria of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society/Latin American Thoracic Association statement [1] and diagnosis was re-confirmed by multidisciplinary discussion.

This study was approved by the Institutional Review Board of the Asan Medical Center (2018-0706) and the requirement for informed consent was waived due to the retrospective nature of this study.

Clinical data

Clinical and survival data for all patients were retrospectively obtained from medical records of the Asan Medical Center and records of the National Health Insurance Service of Korea. Spirometry was performed, and D_{LCO} and total lung capacity by plethysmography were measured according to ERS/ATS recommendations [14–16]. The 6-min walk test was performed according to ERS/ATS guidelines [17, 18]. Personal addresses were obtained based on patients' statements.

Individual-level air pollution concentration

We estimated individual-level concentrations of PM_{10} and NO_2 at geocoded residential addresses of 1114 patients using a previously developed air pollution prediction model in South Korea (figure 1a and b). The details of the prediction model are described elsewhere [19]. In brief, this pointwise spatial prediction model aimed to predict the annual average concentrations of $PM_{10,}$ and NO_2 at any location in South Korea. The model was developed in a universal kriging framework comprising geographic characteristics and spatial correlation based on regulatory monitoring data at approximately 300 monitoring sites over South Korea. Geographic characteristics were identified based on more than 300 geographic variables, which represent potential air pollution sources such as traffic and land use [19]. Our prediction model showed fair and good performance with cross-validated R^2-values of 0.45 and 0.82 for PM_{10} and NO_2, respectively [20]. These R^2-values were consistent with those of previous national or regional models in Western Europe [21] and the USA [22].

Individual long-term exposure to PM_{10} and NO_2 in our study was assessed as predicted annual average concentrations in 2006. We used the concentrations predicted in 2006 as this is 1 year prior to the first

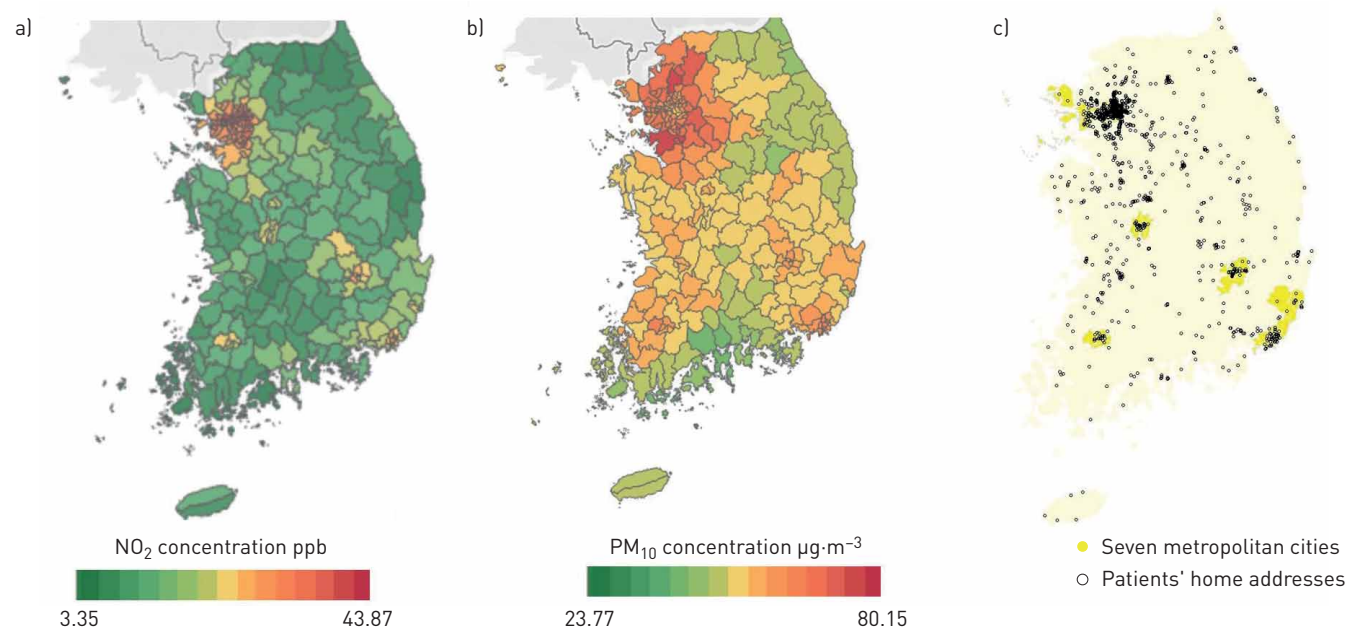

FIGURE 1 Spatial distribution of air pollutants and residential addresses of patients with idiopathic pulmonary fibrosis in South Korea: a) predicted concentration of nitrogen dioxide (NO_2) in 2006, b) predicted concentration of particulate matter with a 50% cut-off aerodynamic diameter of 10 μm (PM_{10}) in 2006 and c) distribution of residential addresses of patients.

death among patients with IPF included in this study observed in 2007. This approach helps to avoid possible overestimation of mortality effects resulting from a decrease of air pollution concentration over time as shown in a previous study of particulate matter and mortality [23]. In line with the decreasing trend in air pollution as observed in most countries, people who survived were assigned to lower air pollution concentrations at the end of the study compared with those who died during the follow-up period, leading to an overestimation of the mortality effects. In South Korea, PM_{10} and NO_2 concentrations decreased from 51 to 41 μg·m^{-3} and from 23 to 20 ppb between 1999 and 2018, respectively (www.airkorea.or.kr). Although our application of a 1-year average to long-term average exposure could have induced exposure misclassification, the modest to high correlation of the annual average concentrations in 2006 with each year during 2001–2016 (PM_{10}: r=0.5–0.8 and NO_2: r>0.8) based on regulatory monitoring data indicate relatively consistent spatial patterns over time (supplementary figure S1).

Statistical analyses

Death was defined as the primary outcome and lung transplantation was considered an equivalent outcome to death. The follow-up duration was calculated from the date of diagnosis to the date of death, lung transplantation or last follow-up. We examined the probability of survival over time on the basis of the Kaplan–Meier curve and investigated the difference in survival probability among the patients in the quartiles of air pollutant concentrations using a log-rank test. To assess the impact of PM_{10} and NO_2 on mortality in IPF, we used a Cox proportional regression model and estimated the hazard ratios for a 10 μg·m^{-3} increase in PM_{10} and a 10 ppb increase in NO_2. Here, we used four health analysis models including different sets of confounders. Model 1 only included PM_{10} or NO_2 concentration. In Model 2, we adjusted for age, sex and diagnosis year. In Model 3, we added individual-level variables at the time of diagnosis, including BMI, smoking status (ever-smoker *versus* never-smoker), lung function (FVC and D_{LCO}) and treatment (antifibrotic agents, steroids with or without immunosuppressants and no treatment). As our primary model, Model 4 additionally included two area-level variables to account for the impact of area-level socioeconomic characteristics that were reported as confounders in previous studies [24, 25]. These variables were the proportion of educational attainment equal to or higher than high school and Gross Regional Domestic Product (GRDP) in each residential district, representing regional educational levels and income that were most commonly applied as socioeconomic status indicators in previous studies [24, 25]. The proportion of high school graduates was obtained from the Korean Statistical Information Service (KOSIS; http://kosis.kr) 2000 Census, while GRDP was obtained from the KOSIS General Statistics in 2005. Subgroup analysis was performed by age (≥65 *versus* <65 years) or sex (male *versus* female). For the sensitivity analysis, we used a two-pollutant model in which one

pollutant (PM_{10} or NO_2) was adjusted for in the analysis of the other pollutant. In addition, we assessed individual exposure incorporating mobility and computed average concentrations across all of the available addresses for each patient rather than the addresses in 2006 used in our primary approach. All statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA) and a p-value <0.05 was considered statistically significant (two-tailed).

Results

Baseline characteristics

Among all subjects, the mean age was 65.7 years, 80.5% were male and 75.9% were ever-smokers (table 1). The annual average concentrations of PM_{10} and NO_2 were 55.9 $\mu g \cdot m^{-3}$ and 22.5 ppb, respectively. Of the patients, 502 (45.1%) lived in seven metropolitan cities (figure 1c). Of the study subject's residential area, the mean±SD rate of educational attainment equal to or higher than high school was 50.9±15.2% and GRDP was 5796.1±3837.0×10^6 USD. During follow-up (median (interquartile range) 3.8 (1.7–6.5) years), 765 patients (68.7%) died and nine patients (0.8%) underwent lung transplantation (median survival period 4.3 years) (supplementary figure S2a).

Association between air pollution and mortality

No significant differences were found in the mortality of the patients with IPF according to the quartiles of NO_2 (p=0.932) and PM_{10} (p=0.382) exposure concentrations (supplementary figure S2b and c). NO_2 was not associated with mortality in the patients with IPF in Models 1–3, where different sets of individual variables were adjusted (Model 1 HR 0.970, 95% CI 0.904–1.041, Model 2 HR 0.990, 95% CI 0.923–1.062 and Model 3 HR 1.000, 95% CI 0.932–1.083) (figure 2). However, there was association in our primary model (HR 1.172, 95% CI 1.030–1.344; p=0.016), Model 4, where all individual- and area-level covariates were adjusted. In both the unadjusted and adjusted models, there was no evidence of association for PM_{10}, although the hazard ratio was higher in Model 4 than in Models 1–3 (figure 2).

Subgroup analysis

In the stratified analysis by age (⩾65 *versus* <65 years) using Model 4, NO_2 was associated with IPF mortality in elderly adults (HR 1.331, 95% CI 1.010–1.598; p=0.010), but not in younger adults (figure 3a). When stratified by sex (male *versus* female), NO_2 showed no association with IPF mortality in both groups (figure 4a). PM_{10} did not show any association with IPF mortality in both age groups and sexes (figures 3b and 4b). When stratified by age and sex, NO_2 was associated with IPF mortality in elderly males (HR 1.305, 95% CI 1.072–1.598; p=0.008), but not in the other three subgroups (figure 5a), whereas PM_{10} exposure was not associated with mortality in any of the subgroups (figure 5b).

Sensitivity analyses

When PM_{10} was additionally included in the primary model (two-pollutant model), NO_2 remained associated with IPF mortality in all patients (HR 1.195, 95% CI 1.030–1.384; p=0.019), in elderly patients

TABLE 1 Baseline characteristics of patients with idiopathic pulmonary fibrosis

Patients	1114
Age years	65.7±8.2
Male	897 (80.5)
Ever-smoker	846 (75.9)
BMI kg·m^{-2}	24.1±3.1
Pulmonary function test	
FVC % pred	70.5±17.6
D_{LCO} % pred	57.3±19.6
TLC % pred	71.2±14.9
Treatment status	
Antifibrotic agents	217 (19.5)
Corticosteroids with or without immunosuppressant	454 (40.8)
None	443 (39.8)
Air pollutant	
PM_{10} $\mu g \cdot m^{-3}$	55.9±5.3
NO_2 ppb	22.5±9.9

Data are presented as n, mean±SD or n (%). BMI: body mass index; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity; PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter of 10 μm; NO_2: nitrogen dioxide.

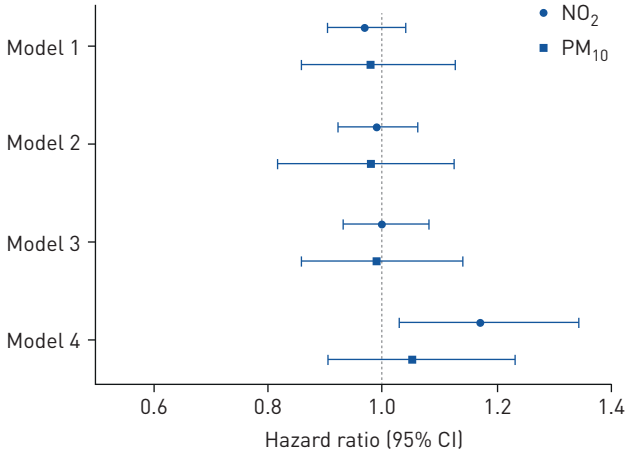

FIGURE 2 Impact of air pollutant concentrations on mortality in all patients with idiopathic pulmonary fibrosis. NO_2: nitrogen dioxide; PM_{10}: particulate matter with a 50% cut-off aerodynamic diameter of 10 µm. Hazard ratio (95% CI) presented per increase of 10 ppb in NO_2 or increase of 10 µg·m^{-3} in PM_{10}. See main text for details of Models 1–4.

(HR 1.370, 95% CI 1.105–1.660; p=0.002) and in elderly males (HR 1.318, 95% CI 1.041–1.660; p=0.021) (supplementary figure S3).

In the analysis using the mean concentrations for all available addresses, NO_2 was associated with mortality in elderly patients (HR 1.195, 95% CI 1.010–1.411; p=0.035) and elderly males (HR 1.207, 95% CI 1.000–1.452; p=0.047) (supplementary figure S4). PM_{10} was not associated with IPF mortality in both analyses (supplementary figures S3 and S4).

Discussion

In our study, we observed an association between air pollution and mortality in patients with IPF using spatially resolved estimates for individual exposure to ambient air pollution. We estimated individual-level concentrations of the air pollutants (PM_{10} and NO_2) at residential addresses of patients with IPF and evaluated the association between air pollutants and mortality. When adjusted for individual- and area-level covariates, NO_2 was associated with mortality in patients with IPF, specifically elderly males. However, we did not find any association for PM_{10}.

The clinical impact of NO_2 exposure in patients with IPF has been reported in previous studies [9, 11, 12]. Johannson *et al.* [9] reported that the occurrence of acute exacerbation was associated with mean (HR 1.41, 95% CI 1.04–1.91; p=0.03) and maximum (HR 1.27, 95% CI 1.01–1.59; p=0.04) concentrations of NO_2 over a 6-week period when adjusted for smoking status and FVC. In another study, Johannson *et al.* [12] also showed a negative association of FVC with average NO_2 concentration during 40 weeks (β= −0.45, 95% CI −0.85– −0.05; p=0.03). These results support our findings as acute exacerbation and low lung function are associated with poor prognosis in patients with IPF [26]. Studies focusing on mortality also reported an association between increased exposure to NO_2 and increased risk of mortality in other respiratory diseases,

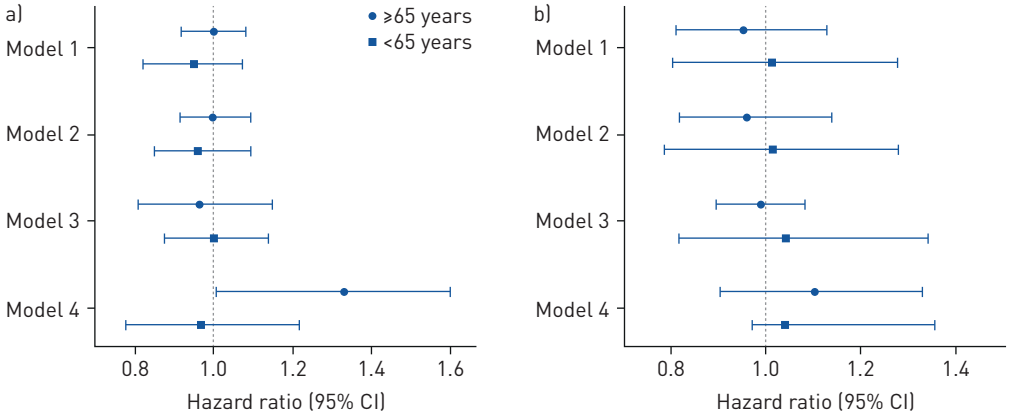

FIGURE 3 Comparison of the impact of air pollutant concentrations on mortality in patients with idiopathic pulmonary fibrosis stratified by age: a) nitrogen dioxide (NO_2) and b) particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}). ≥65 years: n=656; <65 years: n=458. Hazard ratio (95% CI) presented per increase of 10 ppb in NO_2 or increase of 10 µg·m^{-3} in PM_{10}. See main text for details of Models 1–4.

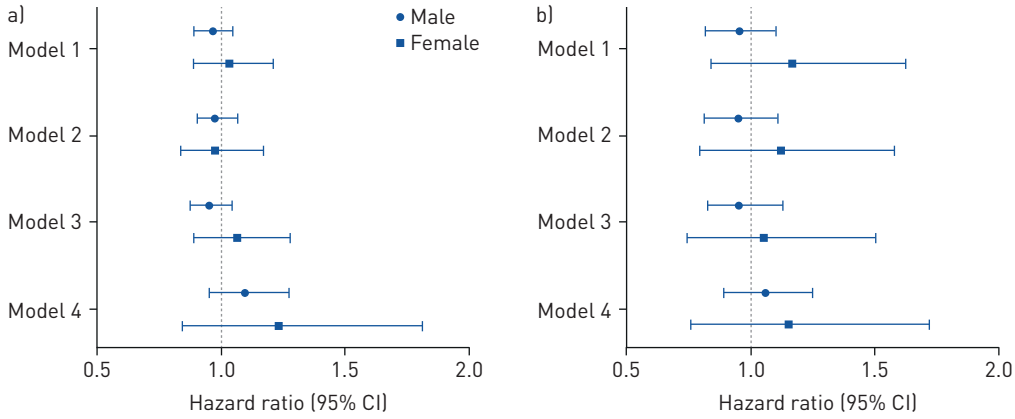

FIGURE 4 Comparison of the impact of air pollutant concentrations on mortality in patients with idiopathic pulmonary fibrosis stratified by sex: a) nitrogen dioxide (NO_2) and b) particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}). Male: n=897; female: n=217. Hazard ratio (95% CI) presented per increase of 10 ppb in NO_2 or increase of 10 µg·m^{-3} in PM_{10}. See main text for details of Models 1–4.

including chronic obstructive pulmonary disease [27], asthma [28] and lung cancer [29]. Inhaled NO_2 is known to induce cell death in type 2 epithelial cells, which is followed by compensatory proliferation of epithelial cells and release of inflammatory factors, ultimately leading to lung fibrosis [30].

Our study found an association with mortality for NO_2 but not for PM_{10}, which is inconsistent with a few previous studies [10, 31, 32]. For example, Sesé *et al.* [10] reported that long-term exposure to PM_{10} (HR 2.01, 95% CI 1.07–3.77; p=0.03) and $PM_{2.5}$ (HR 7.93, 95% CI 2.93–21.33; p<0.001) significantly increased the risk of mortality in patients with IPF, whereas NO_2 did not, when adjusted for age, FVC, D_{LCO} and smoking status. In addition, Abbey *et al.* [31] demonstrated that in the nonsmoking California Seventh-day Adventists Cohort (n=6338), elevated long-term exposure to PM_{10} was related to increasing nonmalignant respiratory mortality (relative risk 1.18, 95% CI 1.02–1.36, for interquartile increases), while long-term NO_2 exposure was not. These inconsistent results may be due to the application of the prediction model based on residential addresses in our study. Outdoor NO_2 is more associated with local sources [33], whereas PM_{10} concentration is associated with widespread regional emissions [34]. Thus, our refined exposure approach based on residential addresses may be suitable for evaluating NO_2 exposure, specifically in the elderly adults who spend most of their time at or near their homes, by reflecting local NO_2 concentrations.

In our study, we found an association between NO_2 and IPF mortality when area-level covariates were considered in addition to individual-level covariates. This finding suggests that area-level covariates are

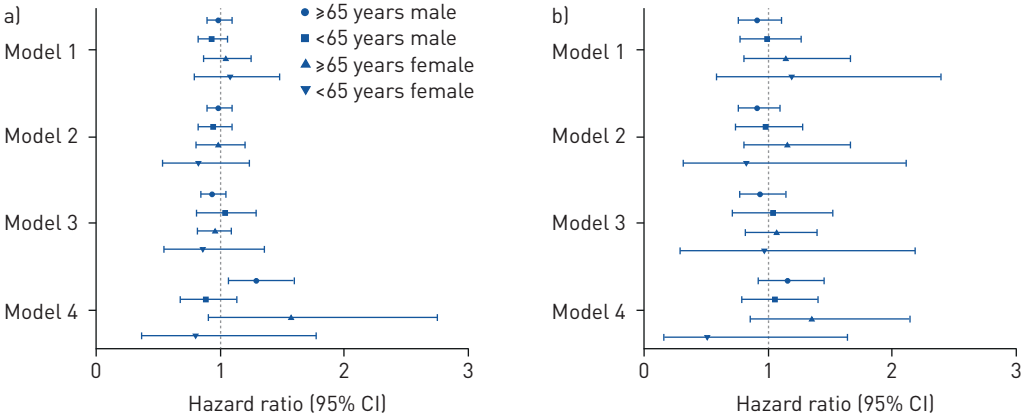

FIGURE 5 Comparison of the impact of air pollutant concentrations on mortality in patients with idiopathic pulmonary fibrosis stratified by age and sex: a) nitrogen dioxide (NO_2) and b) particulate matter with a 50% cut-off aerodynamic diameter of 10 µm (PM_{10}). ⩾65 years male: n=525; <65 years male: n=372; ⩾65 years female: n=131; <65 years female: n=86. Hazard ratio (95% CI) presented per increase of 10 ppb in NO_2 or increase of 10 µg·m^{-3} in PM_{10}. See main text for details of Models 1–4.

important confounders to assess the impact of air pollutants in the nationwide or regional analysis as shown in previous studies [25, 35]. Using the National Health Insurance Service-National Sample Cohort (n=275 337; 2002–2013), KIM *et al.* [25] revealed an increasing trend in hazards ratios of PM_{10} for nonaccidental and cause-specific mortality when area-level covariates were additionally included. CHRISTIDIS *et al.* [35], using the Canadian Community Health Survey-Mortality cohort, also demonstrated that $PM_{2.5}$ exposure was associated with nonaccidental mortality when adjusted for multiple covariates including contextual covariates (*e.g.* ethnic concentrations, census metropolitan area/census agglomeration size and residential instability), whereas the unadjusted model did not show an association. Moreover, BOWE *et al.* [24] demonstrated that $PM_{2.5}$ exposure was positively associated with death due to nonaccidental and noncommunicable diseases after adjusting for several regional variables (*e.g.* population density, area deprivation index, percentage of the population living in a rural area, percentage of the population with limited access to healthy food, percentage of the population with adequate access to exercise opportunities and percentage of adults reporting excessive drinking) in the US veterans cohort.

Similar to previous studies [36–39], our study showed that the elderly were more susceptible to long-term exposure to NO_2 compared with the younger population. CAKMAK *et al.* [36] reported that the risk of NO_2 exposure for mortality was higher in the oldest age group (HR 1.042 (<64 years), 1.083 (65–74 years), 1.120 (75–84 years) and 1.130 (⩾85 years), per interquartile increase; p<0.001) compared with in the general population who lived in seven Chilean urban centres. Additionally, SAMOLI *et al.* [38] showed that the risk of respiratory mortality was higher in areas with a higher proportion of the elderly in 30 European cities. Susceptibility in the older adult population can be explained by several factors such as impaired general status, low socioeconomic status and multiple comorbidities. Moreover, gradual impairment of the DNA repair system in the ageing process [40] may contribute to susceptibility to DNA damage induced by NO_2 exposure [41].

This study has the following limitations. First, this was a retrospective observational study conducted at a single centre, possibly limiting the generalisability of our results. However, the baseline characteristics of our patients were similar to the results in previous reports [9, 10]. Second, since we estimated individual exposures based on residential addresses, exposures at other locations such as workplaces were not considered. Future studies should incorporate exposures from different locations and assess the prognostic impact of air pollution more accurately. Third, although our approach that assessed individual exposure using annual averages for a fixed-year period can avoid possible overestimation of mortality effects, it may not reflect the exposure of each patient during the different follow-up periods since 1995. Fourth, the number of patients in the female group was relatively small, which might have resulted in a lack of power to detect an association in this group. Our findings for the female subgroup of patients with IPF should be confirmed in a larger cohort. Despite these limitations, this study has the following strengths: this study comprised a large number of patients with relatively long-term follow-up periods and evaluated the impact of individual exposure to air pollutants on IPF mortality.

In conclusion, on the basis of individual exposure estimates, our results suggest that increased long-term exposure to NO_2 is significantly associated with mortality in patients with IPF, specifically in elderly males.

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Author contributions: J.W. Song takes full responsibility for the content of this manuscript, including the data and analyses. J.W. Song made substantial contributions to the concept and design of the study. S-Y. Kim developed the design of the methodology. H-Y. Yoon, S-Y. Kim, O-J. Kim and J.W. Song made substantial contributions to the analysis and interpretation of data. H-Y. Yoon, S-Y. Kim and J.W. Song drafted the initial manuscript. All authors discussed the results and reviewed the manuscript.

Conflict of interest: None declared.

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