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ORIGINAL RESEARCH

PM_{10} increases mortality risk in rheumatoid arthritis-associated interstitial lung disease

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ABSTRACT

Objectives The effect of air pollution on the prognosis of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) remains poorly understood. We aimed to evaluate the effect of long-term exposure to particulate matter with an aerodynamic diameter of ≤10 µm (PM_{10}) and nitrogen dioxide (NO_2) on mortality in patients with RA-ILD.

Methods We included 309 patients (mean age, 61.7 years; male, 44.3%) with RA-ILD. Individual-level long-term exposures to PM_{10} and NO_2 at their residential addresses were estimated using a national-scale exposure prediction model. The effect of the two air pollutants on mortality was estimated using a Cox-proportional hazards model adjusted for individual-level and area-level characteristics.

Results The median follow-up period was 4.8 years, and 40.8% of patients died or underwent lung transplantation. The annual average concentrations of PM_{10} and NO_2 were 56.3 µg/m^3 and 22.4 ppb, respectively. When air pollutant levels were stratified by quartiles, no association was observed between air pollutant concentration and mortality in patients with RA-ILD. However, when stratified by two groups (high exposure (top 25th percentile) vs low exposure (bottom 75th percentile)), we observed a significant association between high PM_{10} exposure and mortality (HR 1.68; 95% CI 1.11 to 2.52; p=0.013) but no association between NO_2 exposure and mortality. In the subgroup analyses, the effect of high PM_{10} exposure on mortality was significant in patients aged <65 years (HR 1.98; 95% CI 1.02 to 3.85; p=0.045).

Conclusions Our results indicated that high PM_{10} exposure may be associated with mortality in patients with RA-ILD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Air pollution was previously reported to be positively associated with the incidence of rheumatoid arthritis (RA). However, the effect of air pollution on the prognosis of patients with RA-associated interstitial lung disease (RA-ILD) remains poorly understood.

WHAT THIS STUDY ADDS

⇒ When air pollutant levels were categorized into two groups (high exposure (top 25th percentile) vs low exposure (bottom 75th percentile)), we observed a significant association between mortality and high exposure to particulate matter with an aerodynamic diameter of ≤ 10 µm (HR 1.68; 95% CI 1.11 to 2.52; p=0.013) but not in terms of exposure to nitrogen dioxide.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results indicate that the reduction of air pollution exposure could be helpful in improving the prognosis of patients with RA-ILD.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterised by the progressive destruction of the joints and a variety of extra-articular manifestations, including pulmonary involvement.[1] Interstitial lung disease (ILD) is one of the most common extra-articular manifestations in patients with RA and has an estimated prevalence of 6%–30%.[2 3] The development of ILD was reported to be responsible for 13% of all-cause mortality in patients with RA[4] and showed a median survival of 3 years after diagnosis.[5] Previous studies reported that several risk factors were associated with mortality in patients with RA-associated ILD (RA-ILD), including old age (>60 years old),[6] high titres of rheumatoid factor (RF; >3 * upper limit of normal),[7] lower baseline or a 10% decrease from baseline in forced vital capacity (FVC),[8] and a usual interstitial pneumonia (UIP) pattern on high-resolution CT (HRCT).[9] Air pollution is associated with mortality in chronic respiratory diseases, such as asthma,[10] chronic obstructive pulmonary disease[11] and lung cancer.[12] Moreover, recent studies have reported the associations between air pollution and the clinical course of idiopathic pulmonary fibrosis (IPF) in terms of incidence,[13] acute exacerbation,[14] hospitalisation[15] and mortality.[16 17] However, the effect of air pollution on the prognosis of patients with RA-ILD remains poorly understood.

Anticitrullinated protein antibodies (ACPAs) are a marker for RA autoimmunity, which are produced against citrullinated proteins (CPs) with autoantigenicity,[18] and involved in the development of ILD in patients with RA.[19] CPs are known to be produced in the lungs via inhaled toxic stimuli, such as smoking, in individuals carrying the human leucocyte antigen DR-shared epitopes, which are associated with the risk of ACPA-positive RA.[20] Furthermore, CPs were found in the lung lavage fluid of smokers and the lung parenchymal tissues and synovium of patients with RA-ILD.[21] Considering that ACPAs are often detected before joint symptoms appear, the lung may be the origin of ACPA production.[22] Air pollution was known to be associated with ACPA positivity,[23] which is a risk factor for RA-ILD progression.[6] Furthermore, air pollution was reported to be positively associated with the incidence of RA-ILD,[24] as well as incidence and hospital readmissions of RA.[25 26] On the basis of these findings, we hypothesised that the prognosis of RA-ILD may be associated with exposure to air pollution. Therefore, we aimed to evaluate the effect of long-term exposures to particulate matter with an aerodynamic diameter of ≤10 µm (PM_{10}) and nitrogen dioxide (NO_2) on the mortality in patients with RA-ILD. PM_{10} and NO_2 were estimated at an individual level by using a national-scale air pollution prediction model based on residential addresses.

METHODS

Study population

A total of 313 patients diagnosed with RA-ILD between June 1995 and August 2018 at the Asan Medical Center, Seoul, Republic of Korea, were screened for this study. After excluding participants whose data on baseline characteristics or survival status were not available (n=4), 309 patients were included in this study. A diagnosis of RA was made according to the 2010 American College of Rheumatology/European league against rheumatism criteria by a rheumatologist,[27] and the presence of ILD was confirmed on the basis of HRCT imaging and/or pathological findings.

Clinical data

Clinical and survival data for all patients were retrospectively obtained from medical records and/or the records of the National Health Insurance of Korea. FVC, diffusing capacity of the lungs for carbon monoxide, and total lung capacity were evaluated by spirometry or plethysmography according to the recommendations of the American Thoracic Society/European Respiratory Society.[28–30] The results were expressed as percentages of the normal predicted values. The residential addresses were obtained on the basis of the patients' statements.

HRCT assessment

HRCT scan images were reviewed by a radiologist (JC) and a pulmonologist (SHK) who were blinded to clinical and pathological information. Overall, HRCT patterns were classified as a UIP-like or non-UIP-like pattern on the basis of the HRCT classification of the Fleischner Society Guidelines for the diagnosis of IPF[31] and adjustments were made to allow applicability for patients with RA-ILD.[32] In summary, a UIP-like pattern was defined as a reticular pattern accompanied by honeycombing with or without traction bronchiectasis (or bronchiolectasis) and without considering the distribution or presence of mosaic attenuation, which was suggested by Jacob *et al*.[32] Any disagreements between the two readers were resolved by a third reader (JWS).

Individual-level exposure assessment for PM_{10} and NO_2

On the basis of geo-coded residential addresses, we estimated the individual-level concentrations of PM_{10} and NO_2 by using the validated air pollution prediction model of South Korea (figure 1 A and B). This national-scale pointwise exposure prediction model was developed to estimate the annual average concentrations of PM_{10} and NO_2 at any location in South Korea, and further details can be found in online supplemental appendix S1.[33 34]

The long-term exposure to PM_{10} and NO_2 was assessed by the annual average concentrations estimated in 2006 (1 year before the first event of death in our cohort). The fixed-year exposure could prevent the possible overestimation of air pollution effect on mortality resulting from a substantial decrease in air pollutant concentration over time.[35] In South Korea, PM_{10} concentrations decreased from 51 to 41 µg/m^3, whereas NO_2 concentrations decreased from 23 to 20 parts per billion (ppb) between 1999 and 2018 (https://www.airkorea.or.kr). We considered the average concentrations in 2006 as the long-term average exposure on the basis of the results that the annual average concentrations in 2006 correlated well with those in each year during the 2001–2018 period (PM_{10}: r=0.38–0.84; NO_2: r>0.8) from regulatory monitoring sites. This implied a relatively consistent spatial distribution over time (online supplemental figure S1 and online supplemental figure S2). Furthermore, to overcome bias regarding changes in the residential addresses of each patient, we calculated the individual exposure by estimating the mean concentration in 2006 to reflect all the available addresses of each patient during the study period.

Statistical analyses

The primary outcome of this study was death, and lung transplantation was considered an equivalent event to death. The duration of follow-up was estimated from the date of ILD diagnosis to the date of death, lung transplantation, or time of censoring (31 December 2019). The annual average air pollutant concentrations were categorised into four groups on the basis of quartiles (Q1–Q4). Furthermore, air pollutant concentrations were categorised into two groups to evaluate the effect of high exposure to air pollutants (denoted as Q4, top 25th percentile) compared with low exposure to air pollutants (denoted as Q1–Q3, bottom 75th percentile).[36] The Kaplan-Meier survival curve analysis was used to evaluate

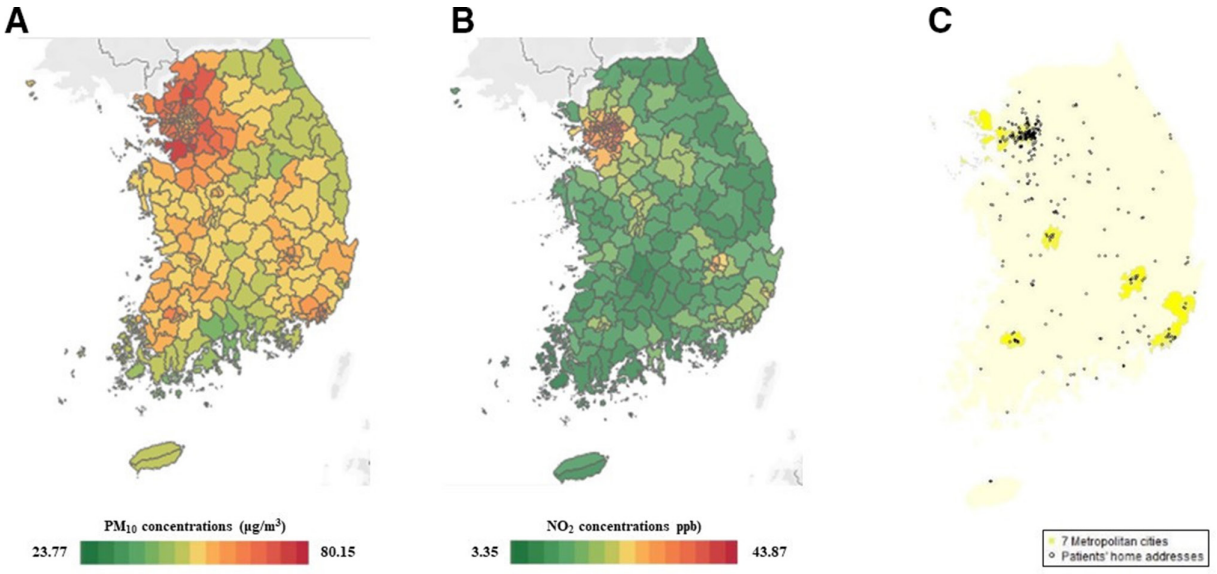

Figure 1 Spatial distribution of air pollutants and the residential addresses of patients with RA-ILD. The map of estimated concentration of PM_{10} (μg/m^3) (A) and NO_2 (ppb) (B) in 2006. The map of the distribution of the residential addresses of patients with RA-ILD (C). RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PM_{10}, particulate matter ≤10 μm; NO_2, nitrogen dioxide.

the survival probability over time, and a log-rank test was used to identify the difference in survival. The Cox-proportional hazards model was used to evaluate the effect of air pollution on the mortality in patients with RA-ILD.

To evaluate the effect of air pollution on mortality according to progressive adjustment, four models with different sets of confounders were used. Model 1 was an unadjusted model that only included PM_{10} or NO_2 concentrations (quartiles; high vs low exposure). In model 2, we adjusted for age, sex and date of ILD diagnosis. In model 3, we added individual-level variables at the time of ILD diagnosis, including smoking status (ever-smokers vs non-smokers), baseline lung function (FVC), and HRCT patterns (UIP-like vs non-UIP-like patterns). In model 4, which was our primary model, we added area-level variables, the proportion of educational attainment equal to or higher than high school, and gross regional domestic product (GRDP) (top 50th percentile vs bottom 50th percentile) in each residential district; these were the most common indicators reflecting socioeconomic status.[37] In the current study, data on the proportion of high school graduates were obtained from the 2000 census (Korean Statistical Information Service (KOSIS) 2000, http://kosis.kr), whereas data on GRDP were collected from the 2005 general statistics (KOSIS 2005).

The subgroup analyses were performed according to age (≥65 years vs <65 years), sex (male vs female) and autoantibody positivity. For sensitivity analysis, the two-pollutant model was used; this model simultaneously included both pollutants (PM_{10} and NO_2) in the analysis to adjust for influences between the two air pollutants. Furthermore, we calculated the individual exposures to air pollution by using single residential addresses close to the year 2006, which reflected the exposure in 2006 more accurately. All statistical analyses were performed using the Statistical Package for the Social Sciences V.24.0 (IBM Corp.). Statistical significance was set at a p value (two-tailed) less than 0.05 ($p<0.05$).

RESULTS

Baseline characteristics

Among the patients, the mean age was 61.7 years, 44.3% were male, and 65.4% had a UIP-like pattern on HRCT (table 1). The annual average concentrations of PM_{10} and NO_2 were 56.3 μg/m^3 and 22.4 ppb, respectively. Among the 309 patients, 148 (47.9%) lived in 7 metropolitan cities (figure 1C). During the follow-up period (median, 4.8 years (IQR 2.8–8.5 years)), 125 (40.5%) patients died, and 1 (0.3%) patient underwent lung transplantation (median survival period, 9.8 years; 5-year survival, 68.6%; online supplemental figure S3–A).

Association between air pollution and mortality

PM_{10} exposure concentrations were divided into four quartiles: Q1 (≥42.10 and < 52.67 μg/m^3), Q2 (≥52.67 and <56.86 μg/m^3), Q3 (≥56.86 and <59.64 μg/m^3) and Q4 (≥59.64 and ≤77.7 μg/m^3). No significant differences were observed in the mortality of patients with RA-ILD between the quartiles of PM_{10} exposure concentrations (p=0.799) (online supplemental figure S3-B). NO_2 exposure concentrations were also classified as Q1 (≥3.83 and <14.78 ppb), Q2 (≥14.78 and <22.25 ppb), Q3 (≥22.25 and <29.68 ppb) and Q4 (≥29.68 and ≤44.10 ppb). No significant differences were observed in the mortality of patients with RA-ILD between the quartiles of NO_2 exposure concentrations (p=0.559) (online supplemental figure S3-C). In both unadjusted and adjusted models, PM_{10} and

Table 1 Baseline characteristics of patients with rheumatoid arthritis-associated interstitial lung disease

	Total
Number	309
Age	61.7±10.3
Male	137 (44.3)
Ever smokers	139 (45)
BMI, kg/m^2	23.5±3.1
Pulmonary function test	
FVC, % predicted	74.2±18.0
DLco, % predicted	63.4±19.5
A UIP-like pattern on HRCT	202 (65.4)
Treatment status	
Corticosteroid with/without IS	198 (64.3)
None	110 (35.7)
RF positive (n=305)	250 (82)
ACPA positive (n=289)	237 (82)
Rate of educational attainment equal to or higher than high school, %	56.6±9.9
GRDP, one million dollars	7689.73 (3018.52–9282.67)
Air pollutants	
PM_{10}, µg/m^3	56.3±5.1
NO_2, ppb	22.4±9.0

Data are presented as mean±SD, median (IQR), or number (%).
USD 1=KRW 1086.50 (15 January 2021).
ACPA, anticitrullinated protein antibodies; BMI, body mass index; DLco, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; GRDP, gross regional domestic product; HRCT, high-resolution CT; ILD, interstitial lung disease; IS, immunosuppressant; NO_2, nitrogen dioxide; PM_{10}, particulate matter≤10 µm; RF, rheumatoid factor; UIP, usual interstitial pneumonia.

NO_2 were not associated with mortality in patients with RA-ILD (online supplemental figure S4).

Furthermore, we evaluated the effect of high concentrations of air pollutants by dividing the PM_{10} exposure concentrations on the basis of Q4 levels (high: PM_{10}≥59.64 µg/m^3 vs low: <59.64 µg/m^3); no significant difference was observed in the mortality of patients with RA-ILD between the two groups (median survival, 7.9 years (95% CI 4.9 to 10.8 years) vs 9.9 years (7.8 to 12.0 years); p=0.350) (figure 2A). High exposure to PM_{10} showed an HR>1 for mortality in model 1 (HR 1.20; 95% CI 0.82 to 1.77; p=0.351) and model 2 (HR 1.45; 95% CI 0.98 to 2.16; p=0.065) without statistical significance. However, when individual-level and/or area-level covariates were adjusted, a statistically significant association was observed between high exposure to PM_{10} and mortality in model 3 (HR 1.60; 95% CI 1.07 to 2.38; p=0.021) and our primary model (model 4: HR 1.68; 95% CI 1.11 to 2.52; p=0.013) (figure 3). In terms of NO_2, no significant difference was noted in the mortality of patients with RA-ILD between the high-concentration and low-concentration groups of NO_2 (median survival, 9.3 years (95% CI 7.9 to 10.8 years) vs 9.8 years (6.7 to 13.0 years); p=0.283) (figure 2B). We could not observe any evidence of association with mortality in both the unadjusted and adjusted models (figure 3).

Subgroup analyses

In the analysis of the data stratified by age (≥65 years vs <65 years) using the primary model, high exposure to PM_{10} was associated with mortality in patients with RA-ILD aged <65 years old (HR 1.98; 95% CI 1.02 to 3.85;

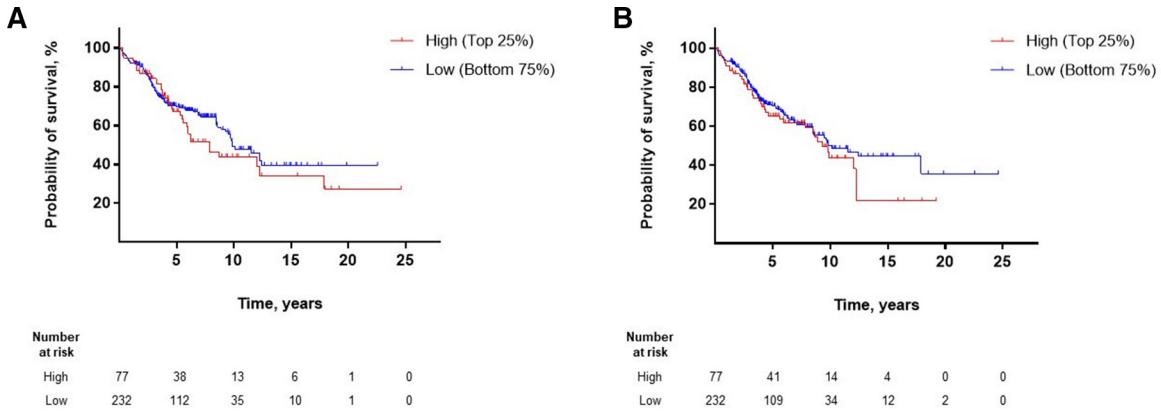

Figure 2 Comparison of survival probability over time between the high-concentration group (top 25th percentile) and the low-concentration group (bottom 75th percentile) among patients with RA-ILD. (A) The Kaplan-Meier survival curve for PM_{10}. (B) The Kaplan-Meier survival curve for NO_2. RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PM_{10}, particulate matter≤10 µm; NO_2, nitrogen dioxide.

p=0.045) (figure 4A). By contrast, an association with NO_2 was not detected in either age group (figure 4B). When the data were stratified by sex (male vs female), high PM_{10} exposures were not associated with RA-ILD mortality in either groups (figure 5A). Conversely, high exposure to NO_2 was significantly associated with mortality in female patients with RA-ILD (HR 2.01; 95% CI 1.02 to 3.96; p=0.044) (figure 5B).

When the data were stratified by autoantibody positivity (RF, ACPA) (online supplemental table S1–S2), high PM_{10} exposure showed a numerical trend towards a positive association with RA-ILD mortality in the RF (+) (HR 1.54; 95% CI 0.98 to 2.42; p=0.060) and ACPA (+) (HR 1.58; 95% CI 0.99 to 2.51; p=0.054) groups; but with marginal significance. High PM_{10} exposure was also associated with mortality in RA-ILD in the RF (−) group (HR 18.81; 95% CI 2.91 to 121.61; p=0.02). Conversely, high NO_2 exposure was not associated with RA-ILD mortality in either autoantibody (+) group.

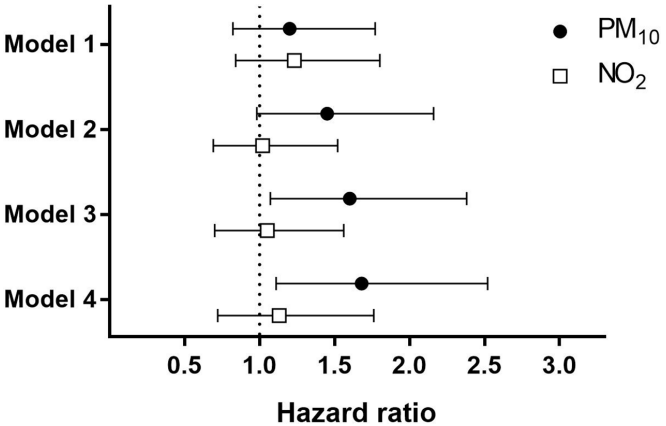

Figure 3 The effect of high (top 25th percentile) air pollutant concentrations on the mortality in patients with RA-ILD. Symbols and error bars represent HRs and 95% CIs, respectively. RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PM_{10}, particulate matter ≤10 µm; NO_2, nitrogen dioxide.

Sensitivity analysis

When both PM_{10} and NO_2 were included in the primary model (two-pollutant model), high PM_{10} exposure was significantly associated with mortality in patients with RA-ILD (HR 1.67; 95% CI 1.10 to 2.52; p=0.015) (online supplemental figure S5). In the analysis using the average concentrations for single residential addresses close to 2006, high PM_{10} exposure demonstrated a numerical trend of positive association with RA-ILD mortality; however, this was not statistically significant (HR 1.32; 95% CI 0.88 to 1.99; p=0.183) (online supplemental figure S6). High exposure to NO_2 was not associated with RA-ILD mortality in both of these analyses (online supplemental figures S5 and S6).

DISCUSSION

To the best of our knowledge, this is the first study to report the association between air pollution and mortality in patients with RA-ILD by using spatially resolved estimates for individual exposures to air pollution. When data were analysed based on quartiles, we could not observe any association between air pollutant concentrations and mortality in patients with RA-ILD. In contrast, we observed that high PM_{10} exposure significantly increased the risk of mortality in the multivariable analysis adjusted by the individual-level and/or area-level covariates. The subgroup analyses demonstrated a significant association between high PM_{10} exposure and mortality in patients with RA-ILD aged <65 years, as well as between high exposure to NO_2 and mortality in the female group.

We did not observe a significant association between air pollutants and mortality in patients with RA-ILD as a whole. This is contrary to previous studies on the effect of air pollutants on mortality in patients with IPF.[16 17] Sese *et al* studied 192 patients with IPF and reported that the increased exposure levels of PM_{10} were significantly associated with all-cause mortality (HR 2.01; 95% CI 1.07 to 3.77; p=0.03).[16] A possible explanation for the

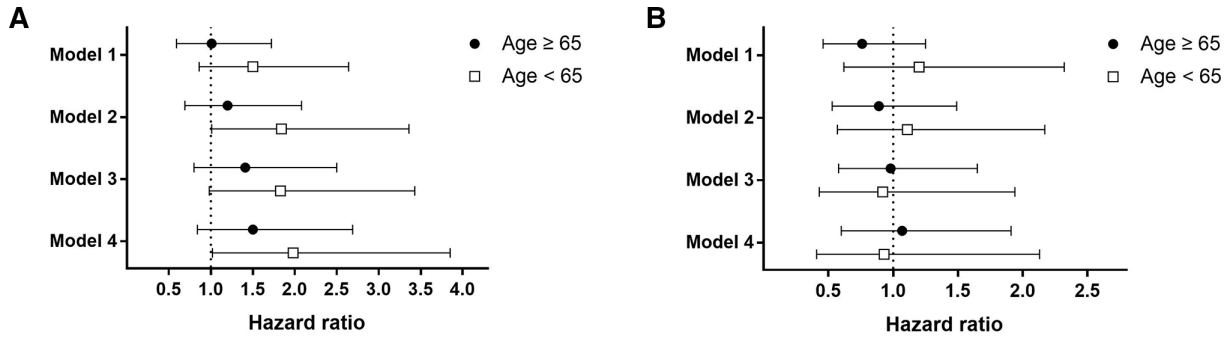

Figure 4 Comparison of the effect of high (top 25th percentile) air pollutant concentrations on mortality in patients with RA-ILD stratified by age*. * ≥65 years (n=137) versus <65 years (n=172). The forest plot of (A) PM_{10} and (B) NO_2. Symbols and error bars represent HRs and 95% CIs, respectively. RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PM_{10}, particulate matter ≤10 µm; NO_2, nitrogen dioxide.

discrepancy could be physical inactivity due to painful arthritis, which may lead to lower exposure to outdoor air pollutants.[38] This is consistent with our results. When data were stratified according to age, high exposure to PM_{10} was associated with an increased risk of mortality in patients with RA-ILD aged <65 years old, who were more physically active. Furthermore, chronic injuries to the alveolar epithelium by air pollution may lead to higher susceptibility to IPF, which is characterised by alveolar epithelium dysfunction.[39] In contrast, RA-ILD is characterised by local and systemic inflammation secondary to ACPA and inducible bronchus-associated lymphoid tissues.[19] Overall, our results suggested that patients with RA-ILD may be less affected by air pollutants than patients with IPF.

Interestingly, high exposure to PM_{10} was significantly associated with an increased risk of mortality in patients with RA-ILD. The clinical effect of PM_{10} has been mostly reported in patients with IPF.[16 40] In addition to its effect on mortality,[16] Winterbottom *et al* reported that each 5 µg/m^3 increase in PM_{10} was associated with a 46 cc/year decline in FVC (p=0.008).[40] Particulate matter is known to induce toxic effects by triggering free radical reactions causing oxidative stress and telomere shortening, leading to the development of chronic respiratory disease, such as ILD, and ultimately increasing mortality.[41] RA-ILD shares some common features with IPF,[39] including a higher prevalence of UIP-like pattern on HRCT scans,[42] the presence of *MUC5B* promoter variant rs35705950,[43] and short telomere length.[44] Therefore, the effect of PM_{10} on IPF could be reproduced in RA-ILD, particularly in those exposed to high concentration of PM_{10}. Furthermore, in contrast to our results, the long-term effect of PM_{10} in the Korean National Health Insurance Service-National Sample Cohort, using the same prediction model as in our study, showed only a marginal association with non-accidental mortality in the general population (HR 1.05; 95% CI 0.99 to 1.11).[37] This suggests that patients with RA-ILD may be more susceptible to PM_{10} than the general population.

Although NO_2 exposure was not associated with mortality in patients with RA-ILD for the whole population in our study, high exposure to NO_2 was associated with an increased risk of mortality in female patients. Different health effects of NO_2 according to sex have been recently reported in the Canadian general population. Shin *et al* reported a significant association between NO_2 and all-cause mortality in women during the cold season (0.7% per 10 ppb increase; 95% CI 0.2 to 1.2) compared with that in men (0.1% per 10 ppb increase; 95% CI −0.8 to −0.9).[45] This may be due to sex-based biologic differences (eg, hormone and lung size), which can influence

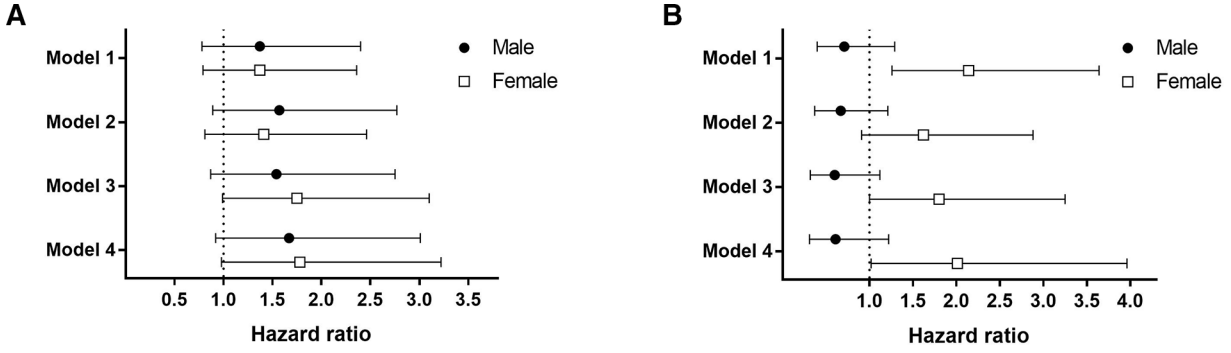

Figure 5 Comparison of the effect of high (top 25th percentile) air pollutant concentrations on mortality in patients with RA-ILD stratified by sex*. *Male (n=137) versus female (n=172). The forest plot of PM_{10} (A) and NO_2 (B). Symbols and error bars represent HRs and 95% CIs, respectively. RA-ILD, rheumatoid arthritis-associated interstitial lung disease; PM_{10}, particulate matter ≤10 µm; NO_2, nitrogen dioxide.

the deposition and transport of air pollutants.[46] In addition, gender-based differences in social roles, such as greater household responsibilities among women, could contribute to increased exposures to indoor NO_2 in women because indoor NO_2 levels may increase through the use of gas stoves in the kitchen and indoor ventilation, as well as exposure to outdoor NO_2.[47 48] Thus, women could be exposed to higher daily concentrations of NO_2 considering their social role, potentially increasing their susceptibility to high exposure to outdoor NO_2.

Our study had several limitations. First, this study was conducted in a single centre, using a retrospective design, which introduced a possibility of selection bias. However, the baseline characteristics of patients in our study were similar to those in previous studies,[7 8] and the residential address of patients with RA-ILD was distributed throughout the country (figure 1C). Second, the sample size was relatively small, which could lead to statistical insignificance. Future studies with a larger number of patients are warranted to confirm our findings. Third, we did not consider the other potential location of air pollutant exposures, such as workplaces, which may affect individual exposure, particularly in patients who spend less time in their homes. Future studies that consider these aspects should be performed to assess the individual effect of air pollution more precisely. Lastly, our approach may not reflect the exact exposures of each patient during years other than 2006. We estimated individual exposures by using annual averages for a fixed-year period to avoid the possible overestimation of mortality effects. However, the annual average concentrations demonstrated relatively consistent spatial patterns over time.

In conclusion, our results suggested that exposure to high concentrations of PM_{10} may be associated with mortality in patients with RA-ILD, particularly in younger patients. Therefore, preventive measures to reduce exposure to high levels of PM_{10} need to be considered to reduce the risk of mortality in patients with RA-ILD.

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Contributors JWS takes full responsibility for the content of this manuscript as the guarantor, including the data and analyses. JWS made substantial contributions to the concept and design of the study. S-YK developed the design of the methodology. All authors made substantial contributions to the analysis and interpretation of data. SHK, S-YK and JWS drafted the initial manuscript. All authors provided a critical review of the manuscript and approved its contents and submission.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. This study was approved by the Institutional Review Board of the Asan Medical Center (2021-1266), and the requirement for informed consent was waived because of the retrospective nature of this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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REFERENCES

1 Scott DL, Wolfe F, Huizinga TWJ. Rheumatoid arthritis. *Lancet* 2010;376:1094–108.
2 Brito Y, Glassberg MK, Ascherman DP. Rheumatoid Arthritis-Associated Interstitial Lung Disease: Current Concepts. *Curr Rheumatol Rep* 2017;19:79.
3 Koo S-M, Kim SY, Choi SM, *et al*. Korean Guidelines for Diagnosis and Management of Interstitial Lung Diseases: Part 5. Connective Tissue Disease Associated Interstitial Lung Disease. *Tuberc Respir Dis* 2019;82:285.
4 Bongartz T, Nannini C, Medina-Velasquez YF, *et al*. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2010;62:1583–91.
5 Koduri G, Norton S, Young A, *et al*. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. *Rheumatology (Oxford)* 2010;49:1483–9.
6 Fu Q, Wang L, Li L, *et al*. Risk factors for progression and prognosis of rheumatoid arthritis-associated interstitial lung disease: single center study with a large sample of Chinese population. *Clin Rheumatol* 2019;38:1109–16.
7 Hyldgaard C, Ellingsen T, Hilberg O, *et al*. Rheumatoid Arthritis-Associated Interstitial Lung Disease: Clinical Characteristics and Predictors of Mortality. *Respiration* 2019;98:455–60.
8 Solomon JJ, Chung JH, Cosgrove GP, *et al*. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2016;47:588–96.
9 Kim EJ, Elicker BM, Maldonado F, *et al*. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2010;35:1322–8.
10 Liu Y, Pan J, Zhang H, *et al*. Short-Term Exposure to Ambient Air Pollution and Asthma Mortality. *Am J Respir Crit Care Med* 2019;200:24–32.
11 DeVries R, Kriebel D, Sama S. Outdoor Air Pollution and COPD-Related Emergency Department Visits, Hospital Admissions, and Mortality: A Meta-Analysis. *COPD* 2017;14:113–21.
12 Cui P, Huang Y, Han J, *et al*. Ambient particulate matter and lung cancer incidence and mortality: a meta-analysis of prospective studies. *Eur J Public Health* 2015;25:324–9.
13 Conti S, Harari S, Caminati A, *et al*. The association between air pollution and the incidence of idiopathic pulmonary fibrosis in Northern Italy. *Eur Respir J* 2018;51.
14 Johannson KA, Vittinghoff E, Lee K, *et al*. Acute exacerbation of idiopathic pulmonary fibrosis associated with air pollution exposure. *European Respiratory Journal* 2014;43:1124–31.
15 Dales R, Blanco-Vidal C, Cakmak S. The Association Between Air Pollution and Hospitalization of Patients With Idiopathic

Pulmonary Fibrosis in Chile: A Daily Time Series Analysis. *Chest* 2020;158:630–6.
16 Sesé L, Nunes H, Cottin V, *et al*. Role of atmospheric pollution on the natural history of idiopathic pulmonary fibrosis. *Thorax* 2018;73:145–50.
17 Yoon H-Y, Kim S-Y, Kim O-J, *et al*. Nitrogen dioxide increases the risk of mortality in idiopathic pulmonary fibrosis. *Eur Respir J* 2021;57.
18 Liu J, Gao J, Wu Z, *et al*. Anti-citrullinated Protein Antibody Generation, Pathogenesis, Clinical Application, and Prospects. *Front Med*;8.
19 Aubart F, Crestani B, Nicaise-Roland P, *et al*. High levels of anti-cyclic citrullinated peptide autoantibodies are associated with co-occurrence of pulmonary diseases with rheumatoid arthritis. *J Rheumatol* 2011;38:979–82.
20 Klareskog L, Stolt P, Lundberg K, *et al*. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. *Arthritis Rheum* 2006;54:38–46.
21 Solomon JJ, Brown KK. Rheumatoid arthritis-associated interstitial lung disease. *Open Access Rheumatol* 2012;4:21–31.
22 Nielen MMJ, van Schaardenburg D, Reesink HW, *et al*. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. *Arthritis Rheum* 2004;50:380–6.
23 Bernatsky S, Smargiassi A, Joseph L, *et al*. Industrial air emissions, and proximity to major industrial emitters, are associated with anti-citrullinated protein antibodies. *Environ Res* 2017;157:60–3.
24 Zhao N, Al-Aly Z, Zheng B, *et al*. Fine particulate matter components and interstitial lung disease in rheumatoid arthritis. *Eur Respir J* 2022;60.
25 Chang K-H, Hsu C-C, Muo C-H, *et al*. Air pollution exposure increases the risk of rheumatoid arthritis: A longitudinal and nationwide study. *Environ Int* 2016;94:495–9.
26 Wu Q, Xu Z, Dan Y-L, *et al*. Association between traffic-related air pollution and hospital readmissions for rheumatoid arthritis in Hefei, China: A time-series study. *Environ Pollut* 2021;268.(Pt A)
27 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
28 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *European Respiratory Journal* 2005;26:319–38.
29 Macintyre N, Crapo RO, Viegi G, *et al*. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J* 2005;26:720–35.
30 Wanger J, Clausen JL, Coates A, *et al*. Standardisation of the measurement of lung volumes. *Eur Respir J* 2005;26:511–22.
31 Lynch DA, Sverzellati N, Travis WD, *et al*. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med* 2018;6:138–53.
32 Jacob J, Hirani N, van Moorsel CHM, *et al*. Predicting outcomes in rheumatoid arthritis related interstitial lung disease. *Eur Respir J* 2019;53.
33 Kim S-Y, Song I. National-scale exposure prediction for long-term concentrations of particulate matter and nitrogen dioxide in South Korea. *Environ Pollut* 2017;226:21–9.
34 Park Y, Song I, Yi J, *et al*. Web-Based Visualization of Scientific Research Findings: National-Scale Distribution of Air Pollution in South Korea. *IJERPH* 2020;17:2230.
35 Ostro B, Hu J, Goldberg D, *et al*. Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study Cohort. *Environ Health Perspect* 2015;123:549–56.
36 Moon DH, Kwon SO, Kim SY, *et al*. Air Pollution and Incidence of Lung Cancer by Histological Type in Korean Adults: A Korean National Health Insurance Service Health Examinee Cohort Study. *Int J Environ Res Public Health* 2020;17:915.
37 Kim OJ, Kim SY, Kim H. Association between Long-Term Exposure to Particulate Matter Air Pollution and Mortality in a South Korean National Cohort: Comparison across Different Exposure Assessment Approaches. *Int J Environ Res Public Health* 2017;14.
38 Sokka T, Häkkinen A, Kautiainen H, *et al*. Physical inactivity in patients with rheumatoid arthritis: data from twenty-one countries in a cross-sectional, international study. *Arthritis Rheum* 2008;59:42–50.
39 Lederer DJ, Martinez FJ. Idiopathic Pulmonary Fibrosis. *N Engl J Med* 2018;378:1811–23.
40 Winterbottom CJ, Shah RJ, Patterson KC, *et al*. Exposure to Ambient Particulate Matter Is Associated With Accelerated Functional Decline in Idiopathic Pulmonary Fibrosis. *Chest* 2018;153:1221–8.
41 Johannson KA, Balmes JR, Collard HR. Air pollution exposure: a novel environmental risk factor for interstitial lung disease? *Chest* 2015;147:1161–7.
42 Tanaka N, Kim JS, Newell JD, *et al*. Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 2004;232:81–91.
43 Juge P-A, Lee JS, Ebstein E, *et al*. MUC5B Promoter Variant and Rheumatoid Arthritis with Interstitial Lung Disease. *N Engl J Med* 2018;379:2209–19.
44 Juge P-A, Borie R, Kannengiesser C, *et al*. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. *Eur Respir J* 2017;49.
45 Shin HH, Maquiling A, Thomson EM, *et al*. Sex-difference in air pollution-related acute circulatory and respiratory mortality and hospitalization. *Sci Total Environ* 2022;806.(Pt 3)
46 Clougherty JE. A growing role for gender analysis in air pollution epidemiology. *Environ Health Perspect* 2010;118:167–76.
47 Matz CJ, Stieb DM, Davis K, *et al*. Effects of age, season, gender and urban-rural status on time-activity: CanadianHuman Activity Pattern Survey 2 (CHAPS 2). *Int J Environ Res Public Health* 2014;11:2108–24.
48 Vardoulakis S, Giagloglou E, Steinle S, *et al*. Indoor Exposure to Selected Air Pollutants in the Home Environment: a Systematic Review. *Int J Environ Res Public Health* 2020;17.