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Original Research

Effects of air pollution on disease activity in patients with rheumatoid arthritis

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ABSTRACT

Objectives: This study aimed to evaluate the associations of air pollution with disease activity and flare rate in patients with rheumatoid arthritis (RA).

Methods: This prospective cohort study included patients with RA who were treated at a tertiary medical centre in South Korea between January 2021 and December 2024. Air pollution exposure was estimated using monthly mean concentrations of 6 air pollutants (sulfur dioxide, nitrogen dioxide, ozone, carbon monoxide, particulate matter $[PM]_{10}$, and $PM_{2.5}$). Disease activity and flares were recorded longitudinally at each outpatient visit. Associations between air pollution and RA disease activity or flare were analysed using linear and logistic generalised estimating equations, adjusting for demographic characteristics, serologic status, medication use, socioeconomic factors, and meteorological variables. As a sensitivity analysis, a case-crossover design using daily air pollutant concentrations preceding each visit was applied, with conditional logistic regression to assess within the same patient.

Results: A total of 12,583 outpatient visits from 1070 patients were analysed. Among 6 pollutants, $PM_{2.5}$ was significantly associated with an increased risk of flare (adjusted odds ratio [OR]: 1.113 [95% CI: 1.017-1.218]) and with higher Disease Activity Score based on 28 joints (DAS28) with C-reactive protein (CRP), Clinical Disease Activity Index, 28-tender joint count, and 28-swollen joint count. In addition, the association between $PM_{2.5}$ and DAS28-CRP was more pronounced among women and nonsmokers. In the case-crossover analysis, prolonged cumulative exposure to $PM_{2.5}$ over >2 weeks was associated with an increased risk of RA flare.

Conclusions: Exposure to air pollutants, particularly $PM_{2.5}$, was associated with increased RA disease activity and flare risk. Further studies are warranted to determine whether improving air quality can reduce disease activity in patients with RA.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- Previous epidemiologic studies have shown an association between air pollution and an increased risk of developing rheumatoid arthritis (RA). However, the effects of air pollution on disease activity and flare occurrence in patients with established RA remain unclear, and the underlying mechanisms have not been fully elucidated.

WHAT THIS STUDY ADDS

- In this prospective cohort study, we demonstrated that higher particulate matter $(PM)_{2.5}$ levels in the air were associated with an increased risk of RA flare and higher disease activity. Prolonged exposure to elevated $PM_{2.5}$ concentrations over >2 weeks was associated with a significantly increased risk of RA flare.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study provides real-world evidence that air pollution, especially $PM_{2.5}$, may be associated with worsening RA disease activity. These findings underscore the importance of healthcare providers and policymakers to recognise its impact on the management of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by symmetric, polyarticular joint inflammation and various extra-articular manifestations. Many factors, including genetics, mucosal inflammation, protein modification, autoantibody production, and environmental exposures, contribute to RA pathogenesis [1,2]. Among these, environmental factors, many of which are modifiable, play a critical role in both the onset and exacerbation of RA. Smoking is a well-established risk factor [3], whereas climatic factors, such as air temperature and humidity, have also been implicated in RA pathogenesis [4].

Air pollution consists of a mixture of gaseous pollutants and particulate matter (PM), which are generated from natural sources and human activities [5]. Major gaseous pollutants include sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO). PM is classified based on aerodynamic diameter, with PM_{10} referring to particles 10 μm or smaller, and $PM_{2.5}$ referring to particles 2.5 μm or smaller. These fine and coarse particles can enter the lower respiratory tract, inducing oxidative stress and promoting systemic inflammatory responses [6,7].

Consistent with these mechanisms, several epidemiologic studies have reported associations between air pollution exposure and an increased risk of developing RA [8–10]. However, the impact of air pollution on disease activity in patients with established RA remains insufficiently investigated.

In this study, we investigate the longitudinal relationship between ambient air pollutants and RA disease activity, aiming to clarify whether fluctuations in environmental exposure contribute to disease aggravation over time.

METHODS

Patients

This prospective cohort included patients diagnosed with RA who were treated at a tertiary medical centre in South Korea between January 2021 and December 2024. All patients met the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA at diagnosis [11]. Among 1118 patients with RA enrolled, those who (i) were followed up for <6 months or (ii) had <3 outpatient visits were excluded (Supplementary Fig S1). For each patient, follow-up began at the first outpatient visit during the study period (defined as the index date) and continued until the earliest of the following events: last outpatient visit, death, or December 31, 2024.

This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB no. H-2105-085-1219) and conducted in accordance with the principles of the Declaration of Helsinki [12]. All patients in the prospective cohort signed written informed consent before any data collection.

Clinical data collection

Baseline demographic characteristics, clinical characteristics, and socioeconomic factors were recorded at the index date. Smoking status, serologic status (seropositive vs seronegative RA), disease duration, and concomitant medications were collected at baseline. In addition, socioeconomic factors, including health insurance type and area deprivation index (ADI), were assessed.

South Korea has a well-established National Health Insurance (NHI) system that provides universal healthcare coverage. Although most individuals are covered by the NHI system, low-income individuals are supported through the Medical Aid (MA) program, which covers approximately 3% of the total population [13]. Health insurance type was categorised as NHI or MA. The ADI at the provincial and municipal levels was reported by the Busan Public Health Policy Institute every 5 years [14,15]. The ADI is a composite score based on 10 socioeconomic indicators designed to quantify relative regional socioeconomic deprivation in South Korea, with higher ADI values indicating greater socioeconomic deprivation. The ADI was constructed using the proportions of the following: (i) households with low socioeconomic status, (ii) households owing a house, (iii) households with poor housing conditions, (iv) individuals with less than a high school education, (v) households without a car, (vi) divorced or widowed individuals, (vii) single-person households, (viii) female-headed households, (ix) older adults (≥65 years), and (x) apartment households. We used the ADI derived from the 2020 Population and Housing Census data.

Clinical data, including patient and physician global assessment, 28-tender joint counts (TJC28) and swollen joint counts (SJC28), and C-reactive protein (CRP) levels, glucocorticoid dose, and use of disease-modifying antirheumatic drugs (DMARDs), were obtained at each follow-up visit. DMARD use was categorised as none, conventional synthetic DMARDs (csDMARDs), or biologic DMARDs (bDMARDs)/targeted synthetic DMARDs (tsDMARDs).

Air pollution data collection

Air pollution data were obtained from the Korea National Institute of Environmental Research. For the main analysis, monthly mean concentrations were collected for the following pollutants: SO_2 (ppb), NO_2 (ppb), O_3 (ppm), CO (ppm), PM_{10} ($\mu g/m^3$), and $PM_{2.5}$ ($\mu g/m^3$). Pollutant data from 17

administrative regions across South Korea were matched to each patient's residential area (Supplementary Fig S2). Although the original Air Quality Index (AQI), in which higher values indicate poorer air quality, is calculated based on 24-hour average values or the maximum 1-hour or 8-hour average values within a 24-hour period, we constructed a modified AQI using monthly mean pollutant concentrations as previously described [16]. Climate variables, including monthly mean air temperature and humidity, were obtained from the Korea Meteorological Administration for the same regions and time periods. To facilitate comparison of the effects of different air pollutants on RA disease activity, all pollutant concentrations were standardised to have a mean of 0 and an SD of 1.

For sensitivity analysis, daily mean air pollution data and climate variables were collected from the same sources.

Outcomes

The main outcome of the study was the occurrence of flare, defined as an increase in Disease Activity Score based on 28 joints with CRP (DAS28-CRP) >1.2 from the previous visit, or >0.6 if the current DAS28-CRP ≥3.2 [17]. Secondary outcomes included TJC28, SJC28, Clinical Disease Activity Index (CDAI), and DAS28-CRP [18].

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

Statistical analysis

Baseline characteristics were summarised as mean ± SD, median (IQR), or counts (%). As most patients returned to the clinic at relatively regular intervals of approximately 3 to 4 months, flare incidence was expressed both as rates per 100 person-years with 95% CIs and as visit-based incidence per 100 outpatient visits. Clinical data from each visit were linked to the corresponding monthly mean air pollution concentrations, based on each patient's residential area and visit month. To assess the association between air pollution and RA disease activity while accounting for within-patient clustering, we used generalised estimating equations (GEEs) with either linear or logistic link functions, as appropriate. Repeated measurements were accounted for by clustering models at the patient level with an autoregressive correlation structure of order 1 [19].

Logistic GEE was used to estimate odds ratios (ORs) with 95% CIs for flare occurrences. For RA disease activity parameters, the β coefficient with 95% CIs was estimated using a linear GEE model. All models were adjusted for prespecified covariates, including age, sex, smoking status, serologic status, time-varying glucocorticoid dose, and DMARD use (none, csDMARDs, or bDMARDs/tsDMARDs), defined according to prescriptions preceding each visit, as well as socioeconomic factors (insurance type and ADI) and meteorological variables (temperature and humidity).

In addition, the association between air pollution and RA disease activity was evaluated across prespecified clinical subgroups defined by clinically relevant factors for RA, such as age, sex, smoking status, comorbidities, baseline concomitant medication for RA, and baseline TJC28 and SJC28 [20−22].

For sensitivity analysis, to better control for time-invariant confounding and to avoid potential reverse causation inherent in the monthly analysis, we conducted a case-crossover study using daily exposure data to further evaluate the association between RA flare and air pollution. In a case-crossover study, exposure levels during a hazard period associated with the outcome are compared with those during a control period within the same individual [23]. Among 1070 patients with RA included in the main analysis, those who experienced at least 1 RA flare during the study period were eligible for the sensitivity analysis (Supplementary Fig S1). For each patient, outpatient visits during the study period were classified as case visits if the visit met the RA flare, whereas all other nonflare outpatient visits within the same individual were defined as control visits. In this visit-based case-crossover design, exposure windows were defined relative to each visit date. The hazard period was defined using variable-width cumulative exposure windows ranging from 1 to 28 days preceding each case visit (eg, lag 1, lag 1-2, lag 1-3, . . ., lag 1-28). Similarly, the control period was defined using the same cumulative exposure windows preceding each control visit. Daily mean air pollution data and meteorological variables, including daily mean temperature and humidity, were assigned to each individual based on their residential area. Conditional logistic regression models were used to estimate the association between air pollution exposure and RA flare within individuals. To account for potential unmeasured time-varying confounding, we adjusted for calendar time using a smooth function, as well as prespecified covariates, including meteorological variables (temperature and humidity) during each exposure window, and time-varying concomitant medications, such as glucocorticoid dose and DMARD use (none, csDMARDs, or bDMARDs/tsDMARDs).

To examine potential nonlinear dose−response relationships between $PM_{2.5}$ concentrations and RA flare, multivariable conditional logistic regression models incorporating restricted cubic splines with 3 degrees of freedom were used.

All statistical analyses were performed using R software (R package: geepack, survival, version 4.4.3), and a P value of <.05 was considered statistically significant. In addition, to evaluate the potential impact of unmeasured confounding, the E-value was calculated to estimate the minimum strength of unmeasured confounding needed to explain an association [24].

RESULTS

Baseline characteristics

A total of 12,583 outpatient visits from 1070 patients were analysed in this study. Baseline demographic and clinical characteristics are summarised in Table 1. Briefly, 86.2% of patients were women, the mean ± SD age was 61.3 ± 12.6 years, and RA duration was 9.1 ± 7.9 years. Baseline median (IQR) DAS28-CRP was 2.4 (1.7-3.3). Patients had a median of 11.0 (9.0-14.0) outpatient clinic visits during 2021 to 2024. Approximately 50% patients used glucocorticoids, with a daily dose of 4.3 ± 2.3 mg of prednisolone equivalent among users. csDMARDs were used in 892 patients (83.4%), and 118 patients (11.0%) received bDMARDs/tsDMARDs, with or without concomitant csDMARDs.

Regional and temporal air pollution trends during the observation period

During the observation period from 2021 to 2024, air pollution levels were generally higher in winter and spring, showing an inverse trend compared with temperature (Fig 1). Regional differences in air pollution were also observed: during the

Table 1
Baseline characteristics of the study population

Characteristics	RA (N = 1070)
Age, y, mean ± SD	61.3 ± 12.6
Sex, female, n (%)	922 (86.2)
Smoker, n (%)	70 (6.5)
Seropositive RA, n (%)	865 (80.8)
Hypertension, n (%)	349 (32.6)
Diabetes mellitus, n (%)	129 (12.1)
Chronic kidney disease, n (%)	35 (3.3)
Interstitial lung disease, n (%)	40 (3.7)
Medical aid, n (%)	26 (2.4%)
Area deprivation index, mean ± SD	−2.6 ± 5.0
RA duration, years, mean ± SD	9.1 ± 7.9
Outpatient clinic visits per patient, median (IQR)	11.0 (9.0-14.0)
TJC28 at index date, median (IQR)	1.0 (0.0-3.0)
SJC28 at index date, median (IQR)	0.0 (0.0-2.0)
DAS28-CRP[a] at index date, median (IQR)	2.4 (1.7-3.3)
Concomitant RA treatment	
Glucocorticoids, n (%)	543 (50.7)
Prednisolone-equivalent,[b] mg/d, mean ± SD	4.3 ± 2.3
csDMARD, n (%)	892 (83.4)
bDMARD/tsDMARD, n (%)	118 (11.0)

bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP, Disease Activity Score based on 28 joints with C-reactive protein; RA, rheumatoid arthritis; SJC28, 28-swollen joint count; TJC28, 28-tender joint count; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

[a] DAS28-CRP at the index date was calculated for 979 patients who had CRP levels available on the index date.

[b] Prednisolone-equivalent dose was presented as mean ± SD among glucocorticoid users only.

spring, Incheon showed the highest levels of SO_2 and CO; Gyeonggi-do and Chungcheongnam-do had the highest levels of PM_{10} and $PM_{2.5}$; and Seoul exhibited the highest concentration of NO_2 (Supplementary Table S1).

The mean ± SD concentrations of air pollutants matched to patient visits during the study period were as followed: SO_2 (ppb), 2.72 ± 0.45; NO_2 (ppb), 17.94 ± 6.87; O_3 (ppm), 0.03 ± 0.01; CO (ppm), 0.41 ± 0.09; PM_{10} (μg/m^3), 34.86 ± 13.23; and $PM_{2.5}$ (μg/m^3), 18.49 ± 6.00. In addition, the modified AQI values matched to patient visits during the study period averaged 68.35 ± 11.51, with the highest in January (83.70 ± 5.12) and lowest in September (51.25 ± 5.91).

Air pollution and RA flare

During the 3235.43 person-years of follow-up, 1278 flare events occurred among 604 patients with RA, corresponding to an incidence rate of 39.5 per 100 person-years (95% CIs: 37.36-41.73) and 10.16 per 100 outpatient visits. Among 12,583 outpatient visits, the monthly ratio of flare events to outpatient visits was highest in January (0.124; 84 flares out of 679 outpatient visits), and lowest in April (0.086; 90 flares out of 1050 outpatient visits) (Supplementary Fig S3).

The risk of RA flare was increased with higher modified AQI (adjusted OR: 1.115 [1.020-1.219]) (Supplementary Table S2). Among the 6 air pollutants examined, $PM_{2.5}$ was significantly associated with an increased risk of flare in the multivariable GEE model (adjusted OR: 1.113 [1.017-1.218]). The point estimate of the E-value for $PM_{2.5}$ was 1.47. PM_{10} and O_3 also showed positive, but nonsignificant associations with flare risk (adjusted ORs: 1.060 [0.980-1.148] and 1.023 [0.934-1.121], respectively) (Fig 2, Supplementary Table S3).

Air pollution and other RA disease activity measures

Higher modified AQI was associated with increased overall disease activity in patients with RA (Supplementary Table S2). In univariable analyses, high $PM_{2.5}$ concentrations were significantly associated with higher TJC28 and SJC28. These associations remained consistent after adjustment for covariates (adjusted β: 0.064 [0.010-0.119] and 0.046 [0.005-0.088], respectively). In addition, higher $PM_{2.5}$ levels were significantly associated with increased DAS28-CRP and CDAI (adjusted β: 0.031 [0.009-0.053] and 0.171 [0.039-0.302], respectively) (Table 2, Supplementary Table S4).

DAS28-CRP increased with high PM_{10} concentrations (adjusted β: 0.020 [0.001-0.039]), and SJC28 increased with high O_3 levels (adjusted β: 0.045 [0.003-0.088]). Among the 6

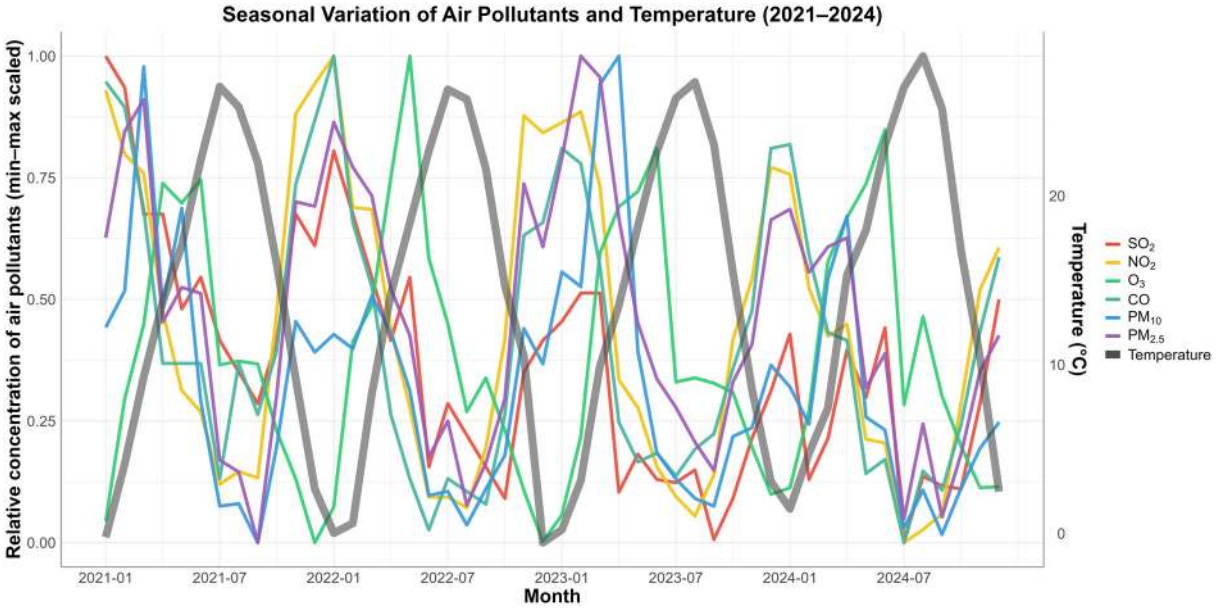

Figure 1. Monthly trends in air pollutants during 2021 to 2024. CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; SO_2, sulfur dioxide.

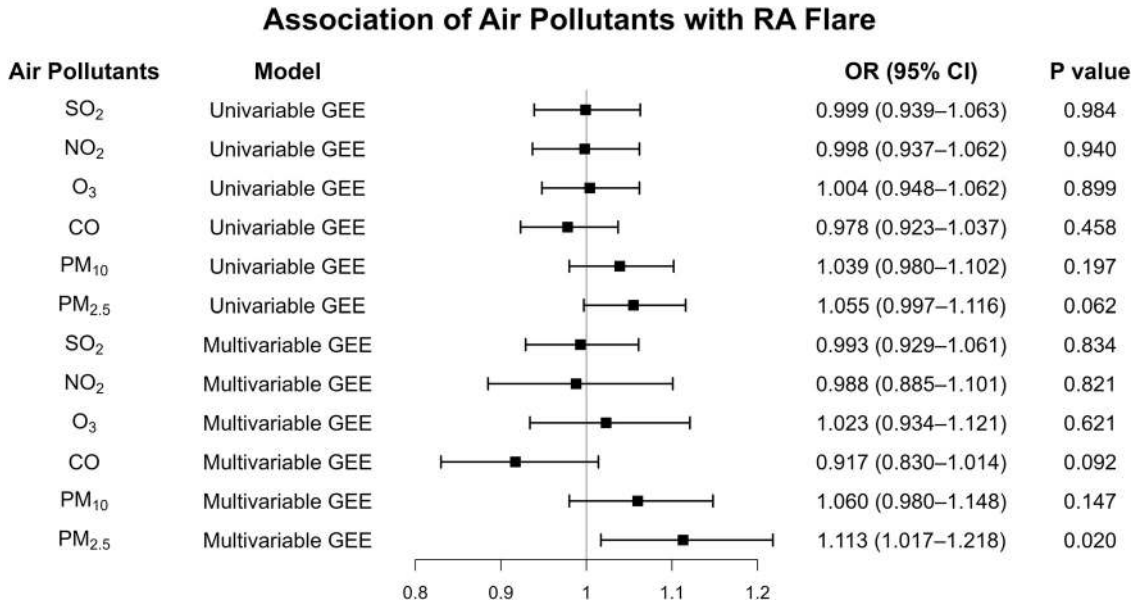

Figure 2. Odds ratios (ORs) for RA flare associated with air pollutants. Results from generalised estimating equation (GEE) models were presented as univariable and multivariable analyses. Multivariable models were adjusted for age, sex, smoking status, serologic status, time-varying concomitant medications (glucocorticoid dose and DMARD use), socioeconomic factors (insurance type and area deprivation index), and meteorological variables (temperature and humidity). Concentrations of air pollutants were standardised to have a mean of 0 and an SD of 1; therefore, effect estimates represent the association per 1-SD increase in monthly mean air pollutant concentrations. CO, carbon monoxide; DMARD, disease-modifying antirheumatic drug; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; RA, rheumatoid arthritis; SO_2, sulfur dioxide.

air pollutants, $PM_{2.5}$ showed the largest effect size and was the only pollutant significantly associated with all disease activity parameters (DAS28-CRP, CDAI, TJC28, and SJC28).

Supplementary Figure S4 presents the predicted disease activity (DAS28-CRP and CDAI) across $PM_{2.5}$ levels, using multivariable GEE with spline smoothing. After adjustment for covariates, both DAS28-CRP and CDAI showed an increasing trend with rising $PM_{2.5}$ levels.

Interaction between $PM_{2.5}$ and clinical factors on RA disease activity

The association between $PM_{2.5}$ and DAS28-CRP was more prominent in female patients (*P* for interaction .026) and non-smoking patients (*P* for interaction .012). In addition, patients with a higher baseline TJC28 (TJC28 ≥2) showed a relatively greater increase in DAS28-CRP with higher $PM_{2.5}$ (Fig 3). In

Table 2
Association of air pollutants with RA disease activity

	DAS28-CRP		CDAI	
	Univariable analysis Crude β (95% CI)	Multivariable analysis[a] Adjusted β (95% CI)	Univariable analysis Crude β (95% CI)	Multivariable analysis[a] Adjusted β (95% CI)
Gas				
SO_2	0.001 (−0.017 to 0.019)	−0.001 (−0.023 to 0.021)	0.016 (−0.088 to 0.121)	0.009 (−0.120 to 0.138)
NO_2	0.004 (−0.010 to 0.017)	0.022 (−0.018 to 0.062)	0.002 (−0.073 to 0.076)	0.109 (−0.139 to 0.358)
O_3	0.003 (−0.008 to 0.015)	0.016 (−0.007 to 0.039)	0.050 (−0.014 to 0.113)	0.129 (−0.003 to 0.261)
CO	−0.003 (−0.015 to 0.009)	−0.015 (−0.044 to 0.013)	−0.018 (−0.086 to 0.050)	−0.017 (−0.183 to 0.148)
Particle				
PM_{10}	0.008 (−0.003 to 0.020)	0.020 (0.001-0.039)	0.032 (−0.035 to 0.099)	0.069 (−0.045 to 0.183)
$PM_{2.5}$	0.012 (−0.000 to 0.024)	0.031 (0.009-0.053)	0.060 (−0.008 to 0.128)	0.171 (0.039-0.302)

	TJC28		SJC28	
	Univariable analysis Crude β (95% CI)	Multivariable analysis[a] Adjusted β (95% CI)	Univariable analysis Crude β (95% CI)	Multivariable analysis[a] Adjusted β (95% CI)
Gas				
SO_2	0.021 (−0.023 to 0.065)	−0.002 (−0.056 to 0.052)	0.035 (0.002-0.068)	0.034 (−0.006 to 0.075)
NO_2	0.022 (−0.009 to 0.053)	0.030 (−0.075 to 0.136)	0.005 (−0.017 to 0.027)	0.018 (−0.060 to 0.095)
O_3	0.005 (−0.021 to 0.032)	0.031 (−0.023 to 0.084)	0.019 (−0.002 to 0.039)	0.045 (0.003-0.088)
CO	0.008 (−0.021 to 0.037)	−0.023 (−0.091 to 0.046)	0.000 (−0.020 to 0.021)	0.000 (−0.053 to 0.053)
Particle				
PM_{10}	0.037 (0.009-0.065)	0.042 (−0.007 to 0.091)	0.020 (−0.000 to 0.040)	0.023 (−0.013 to 0.058)
$PM_{2.5}$	0.041 (0.013-0.070)	0.064 (0.010-0.119)	0.023 (0.003-0.044)	0.046 (0.005-0.088)

CDAI, Clinical Disease Activity Index; CO, carbon monoxide; DAS28-CRP, Disease Activity Score based on 28 joints with C-reactive protein; DMARD, disease-modifying antirheumatic drug; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; RA, rheumatoid arthritis; SJC28, 28-swollen joint count; SO_2, sulfur dioxide; TJC28, 28-tender joint count.
Concentrations of air pollutants were standardised to have a mean of 0 and a SD of 1; therefore, effect estimates represent the association per 1-SD increase in monthly mean air pollutant concentrations.
[a] Adjusted for age, sex, smoking status, serologic status, time-varying concomitant medications (glucocorticoid dose and DMARDs use), socioeconomic factors (insurance type and area deprivation index), and meteorological variables (temperature and humidity).

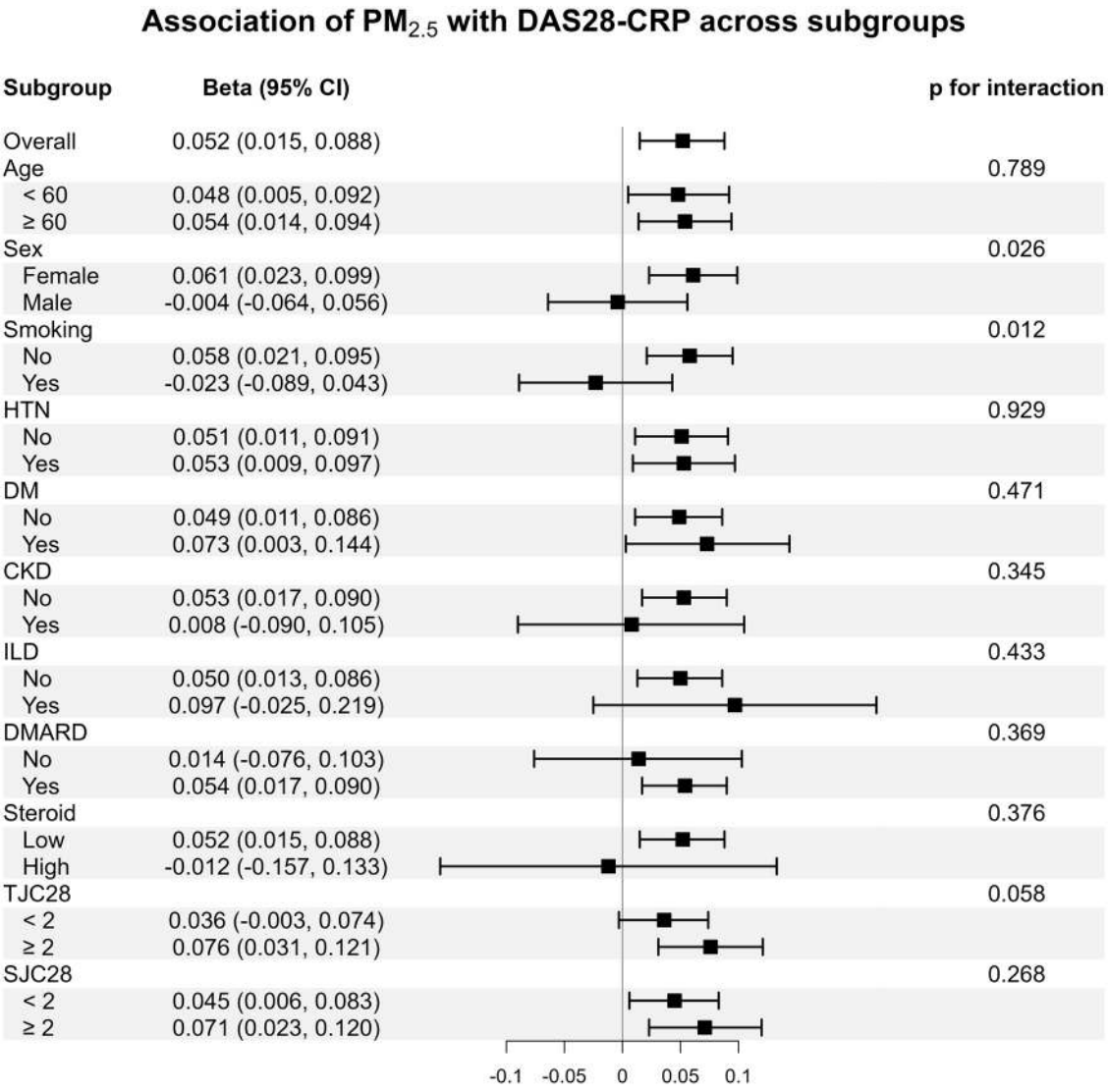

Figure 3. Association of $PM_{2.5}$ with DAS28-CRP across clinical subgroups. High dose of steroid was defined as a daily dose of ≥20 mg of prednisolone. Effect estimates represent the association per 10 μg/m^3 increase in monthly mean $PM_{2.5}$ concentration. Adjusted for age, sex, smoking status, serologic status, time-varying concomitant medications (glucocorticoid dose and DMARD use), socioeconomic factors (insurance type and area deprivation index), and climate variables (temperature and humidity). CKD, chronic kidney disease; DAS28-CRP, Disease Activity Score based on 28 joints with C-reactive protein; DM, diabetes mellitus; DMARD, disease-modifying antirheumatic drug; HTN, hypertension; ILD, interstitial lung disease; PM, particulate matter; SJC28, 28-swollen joint count; TJC28, 28-tender joint count;

contrast, the association of $PM_{2.5}$ with RA flare was not significantly modified by any clinical factors (Supplementary Fig S5).

Sensitivity analysis using case-crossover design

Among 603 patients with RA who experienced at least 1 RA flare, a total of 8024 outpatient visits were included, comprising 1278 case visits and 6746 control visits (Supplementary Fig S1).

Overall, the findings were highly consistent with the main analysis, supporting the robustness of the association between $PM_{2.5}$ exposure and RA flare. Specifically, higher $PM_{2.5}$ exposure was associated with an increased risk of RA flare across most lag periods, except for lag 1 and lag 1 to 7 period (Supplementary Table S5).

Notably, longer cumulative lag periods of daily mean $PM_{2.5}$ exposure preceding each visit were associated with a higher likelihood of RA flare, with more pronounced associations observed when the cumulative lag period extended beyond approximately 14 days (Fig 4A). Exposure−response curves further demonstrated positive dose-dependent associations between $PM_{2.5}$ levels and the risk of RA flare (Fig 4B).

DISCUSSION

In this prospective study, we observed a significant association between ambient air pollution and RA disease activity over 4 years of longitudinal follow-up in patients with RA. Among the evaluated pollutants, $PM_{2.5}$ showed the strongest and most consistent association with RA flare.

Previous studies have focused primarily on the contribution of air pollution to the development of RA rather than to the exacerbation of RA [25]. Although recent research has suggested that air pollution may aggravate RA disease activity [26], findings across studies have been inconsistent. Some reported that exposure to SO_2 and NO_2 was associated with increased DAS28, whereas PM_{10}, O_3, and CO were not [27]. In contrast, another study implicated that O_3 increased DAS28, whereas PM_{10} and NO_2 showed negative associations [28]. Other investigations have shown that CO, NO_2, and O_3 could significantly

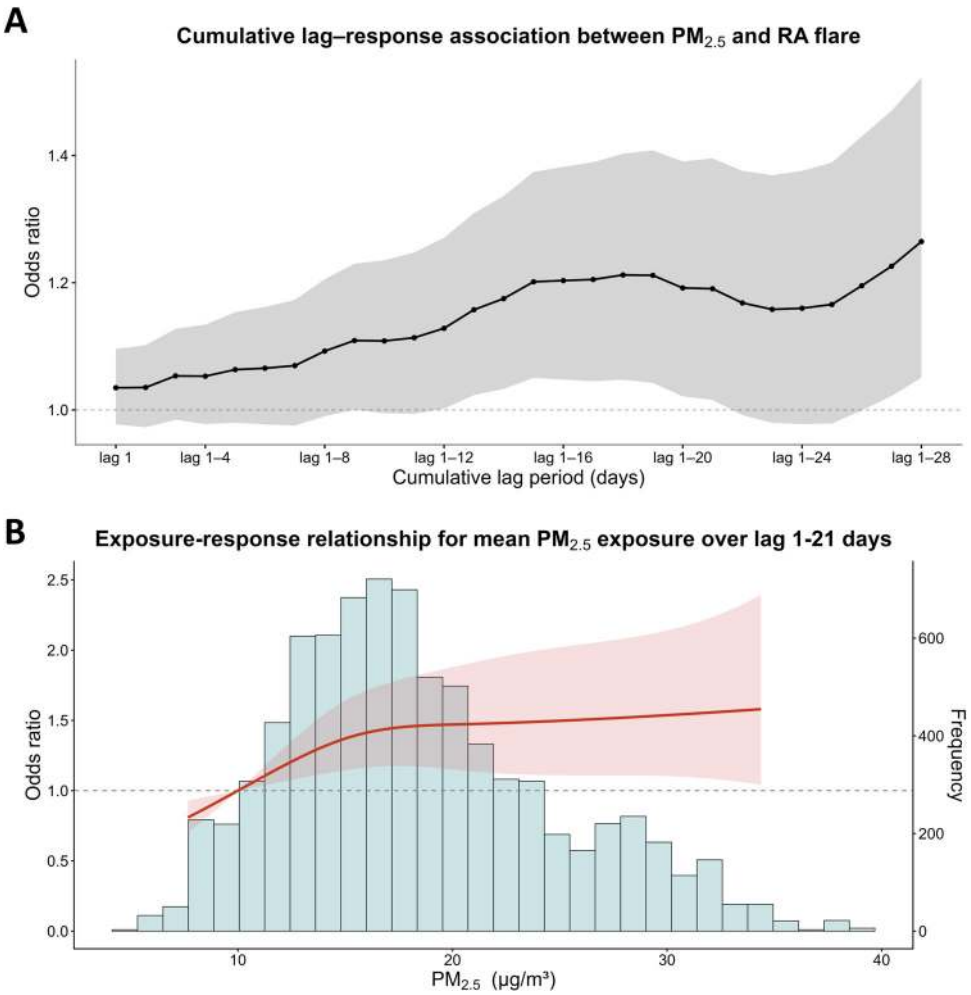

Figure 4. Cumulative $PM_{2.5}$ exposure and the risk of RA flare in the case-crossover cohort. (A), Cumulative lag−response associations across variable-width cumulative lag periods. $PM_{2.5}$ exposure was defined as the mean concentration over each cumulative lag window, with progressively extended lag windows from lag 1 to lag 1-28 days (i.e., lag 1, lag 1-2, lag 1-3, … , lag 1-28). (B) Exposure−response relationship for cumulative $PM_{2.5}$ exposure (lag 1-21 days) estimated using restricted cubic spline models with multivariable conditional logistic regression. Models were adjusted for daily mean temperature and humidity over each corresponding lag period, time-varying concomitant medications (glucocorticoid dose and DMARD use) and calendar time using a smooth function. In panel (A), effect estimates represent the association per 10 μg/m^3 increase in daily mean $PM_{2.5}$ concentration. In panel (B), histograms represent the distribution of $PM_{2.5}$ concentrations. Solid lines indicate adjusted ORs, and shaded areas represent 95% CI. The reference value was set at 10 μg/m^3 for the cumulative lag period. Flare was defined as an increase in DAS28-CRP >1.2, or >0.6 if the DAS28-CRP ≥3.2. DAS28-CRP, Disease Activity Score based on 28 joints with C-reactive protein; DMARD, disease-modifying antirheumatic drug; OR, odds ratio; PM, particulate matter; RA, rheumatoid arthritis.

increase DAS28 [29,30], whereas others found no significant associations [31]. These heterogeneous results may reflect variations in study design, pollutant composition, regional meteorological factors, and patient populations.

Air pollution may influence disease activity through the generation of reactive oxygen species (ROS). ROS can activate nuclear factor kappa B and stimulate the production of tumour necrosis factor-α and interleukin-1, promoting synovial inflammation. Air pollution has been implicated in lung inflammation and the formation of inducible bronchus-associated lymphoid tissue, which may promote the generation of anticitrullinated peptide antibodies. Furthermore, pollutants may directly contribute to joint inflammation and erosion [32−35].

In this study, we identified $PM_{2.5}$ as a key contributor to increased RA disease activity. $PM_{2.5}$ particles are smaller than red blood cells and can penetrate deeply into the respiratory tract, accumulating in alveolar ducts and capillaries, and subsequently disseminate to distant organs through the circulation [36]. These particles can induce ROS production through several pathways: the direct metal−cell interaction [37], increased oxidase activity, and calcium channel activation in the cytoplasmic membrane or endoplasmic reticulum [38], and disruption of mitochondrial homeostasis, leading to mitochondrial DNA damage [39]. Excess ROS can result in DNA damage, oxidative stress, and inflammatory responses in multiple organs [40], which may aggravate synovial and systemic inflammation in RA.

Our subgroup analysis further revealed that sex, smoking status, and baseline TJC28 influenced the association between air pollution and RA disease activity. Specifically, women, nonsmokers, and patients with higher baseline TJC28 showed a stronger association between $PM_{2.5}$ and DAS28-CRP. Similar interactions were observed in chronic obstructive pulmonary disease (COPD), where $PM_{2.5}$ induced airway neutrophilic inflammation predominantly in nonsmokers, suggesting that chronic smoking-related airway inflammation may mask the acute effects of $PM_{2.5}$ [41]. Lungs of nonsmokers, being less chronically inflamed and not repeatedly exposed to irritants, may be more vulnerable to the oxidative and inflammatory effects of ambient $PM_{2.5}$. Because cigarettes contain a much higher concentration of $PM_{2.5}$ than ambient air, smokers may already have maximally activated airway inflammatory pathways. As a result, further exposure to environmental $PM_{2.5}$ may

have a diminished or "saturated" effect on RA disease activity. In contrast, patients with high TJC28 in baseline may represent a more inflammatory state, making them more responsive to additional inflammatory stimuli such as air pollution. This may reflect biological pathways through which $PM_{2.5}$, after translocating from the alveoli into systemic circulation, can amplify pre-existing synovial inflammation.

In the main analysis, we evaluated the association between air pollution and RA disease activity using monthly averaged air pollutant concentrations. Although it can show the overall trends between air pollution and disease activity, it may obscure short-term fluctuations in air pollution that occur between clinical assessments. To address this, we additionally conducted a case-crossover analysis to evaluate temporal associations at the individual level. Notably, short-term increases in $PM_{2.5}$ concentrations were not associated with an immediate increase in RA flare risk. Rather, prolonged exposure to higher $PM_{2.5}$ levels was associated with a significantly increased risk of RA flare, suggesting that cumulative exposure over time may be more relevant than transient peaks in influencing RA disease activity.

South Korea has experienced relatively high levels of ambient air pollution compared with many other Organization for Economic Co-operation and Development (OECD) countries, particularly with respect to $PM_{2.5}$ concentrations. According to OECD reports, South Korea had the highest mean population exposure to $PM_{2.5}$ among OECD countries in 2013 [42]. In addition, the 2024 World Air Quality Report ranked South Korea 55th among 138 countries in annual average $PM_{2.5}$ concentration worldwide [43]. Therefore, given the widespread and persistent exposure to ambient air pollution in South Korea, increases in RA disease activity at the individual level may still have meaningful public health implications.

This study has some limitations. First, actual individual exposure to air pollution may differ from assigned exposure levels. For instance, outdoor activity time and personal behaviours such as mask use and the use of indoor air purification systems vary among individuals, introducing potential unmeasured confounding. Second, we did not have information on relevant lung diseases, such as pneumonia, asthma, or COPD, which might mediate pulmonary inflammatory response to air pollution. Third, the exposure assignment was based on residential area, and discrepancies between residence and workplace locations, as well as relocations during follow-up, may have led to exposure misclassification. Fourth, the estimated E-value suggested that an unmeasured confounder associated with both $PM_{2.5}$ and RA flare >1.47 could potentially explain away the observed association. In addition, as our study included only Korean patients, the generalizability of our findings to other regions with different environmental, geographic, or ethnic backgrounds might be limited. Last but not least, although the observed associations were statistically significant, the effect sizes (ORs and β coefficients) were relatively modest. Given that most patients in our cohort had well-controlled RA, further studies are needed to determine whether the impact of air pollution on disease activity is more pronounced in patients with higher baseline disease activity. In addition, considering the pulmonary and systemic inflammatory effects of air pollution, future studies investigating the association between air pollution exposure and RA-associated interstitial lung disease flare may provide clinically relevant insights.

CONCLUSION

This study provides real-world evidence that higher levels of air pollution, particularly $PM_{2.5}$, are related to worsened RA disease activity and a higher risk of flare. Although further external validation is needed, these findings have important clinical and public health implications. Physicians should encourage patients with RA to minimise exposure to poor air quality, and policymakers should prioritise air quality improvement to reduce the burden of chronic illnesses, including RA flares and elevated disease activity.

Competing interests

EBL received a speaker fee from Boehringer Ingelheim and a consultant fee from Priovant Therapeutics. All other authors declare no competing interests.

CRediT authorship contribution statement

Sung Cheol Jung: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Jeffrey R Curtis:** Writing – review & editing, Formal analysis, Conceptualization. **Seojin Yang:** Writing – review & editing, Investigation, Data curation. **Yunhee Choi:** Writing – review & editing, Methodology, Formal analysis. **Min Hyuk Lim:** Writing – review & editing, Data curation. **Saram Lee:** Writing – review & editing, Data curation. **Sung Ik Cho:** Writing – review & editing, Investigation. **Jin Kyun Park:** Writing – review & editing, Investigation. **Jun Won Park:** Writing – review & editing, Methodology, Investigation. **Eun Bong Lee:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

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Patient consent for publication

All patients gave their written informed consent before their participation.

Ethics approval

This study was approved by the institutional review board at Seoul National University Hospital (IRB No. H-2105-085-1219).

Provenance and peer review

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Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2026.06.018.

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