의학박사 학위논문

만성폐쇄성 폐질환 환자에서 계절별 $PM_{2.5}$ 농도의 영향

Seasonal Effect of $PM_{2.5}$ Exposure in Patients with COPD: a Multicenter Panel Study

울 산 대 학 교 대 학 원

의 학 과

허 진 영

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지 도 교 수　　이 세 원

이 논문을 의학박사 학위 논문으로 제출함

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울 산 대 학 교 대 학 원
의　　학　　과
허 진 영

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심사위원	오연목	(인)
심사위원	홍수종	(인)
심사위원	김남국	(인)
심사위원	김환철	(인)
심사위원	이세원	(인)

울 산 대 학 교 대 학 원

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감사의 글

박사과정을 진행하면서 학위 논문을 작성할 수 있도록 많은 분들의 도움이 있었습니다. 이 글을 통해 감사의 인사를 드리고자 합니다.

먼저 부족한 저를 제자로 받아 주시고 좋은 연구주제를 주시고 지도해주신 이세원 교수님께 깊은 감사의 뜻을 전합니다. 연구자로서 교수님 덕분에 좋은 연구를 할 수 있었고, 연구에 대해 많은 가르침을 주셔서 즐겁게 많이 배웠습니다. 바쁘신 와중에 심사를 맡아 세밀하게 검토하고 지적해 주신 오연목, 홍수종, 김남국, 김환철 교수님께 감사드립니다. 미세먼지 농도 자료를 정리해 주신 인하대학교 직업환경의학과 나근주, Dirga Kumar Lamichhane 선생님, 만성 폐쇄성 폐질환 환자를 모으고 자료를 정리하는데 도움을 주신 이재승, 박신희, 나승원, 강성윤, 정복현, 김미혜, 이상민, 이상표 교수님 감사합니다. 연구를 진행하는 과정에서 개선사항을 지적해 주시고 논문작성에 조언을 해 주신 최창민, 임채만, 김호철 교수님께도 감사의 말씀을 올립니다.

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마지막으로 항상 응원해 주고 옆을 지켜 주신 아내, 딸, 아버지, 어머니, 장인어른, 장모님께 감사의 인사를 드립니다.

2022년 1월

허진영

ABSTRACT

***Background*:**

Exposure to particulate matter of diameter < 2.5 μm ($PM_{2.5}$) is a risk factor of occurrence and worsening chronic obstructive pulmonary disease (COPD). However, most evidence comes from epidemiologic data without individual measurement of $PM_{2.5}$. The levels of PM2.5 are known to vary seasonally, but the seasonal differences in the impact of $PM_{2.5}$ have not been studied. We aimed to investigate how $PM_{2.5}$ impact COPD patients as season change.

Methods:

From 2019 to 2020, 105 COPD patients were followed for one year. Individual indoor and outdoor $PM_{2.5}$ concentrations were monitored continuously, and detailed $PM_{2.5}$ measurements and clinical parameters were assessed trimonthly.

Results

The mean annual indoor and outdoor $PM_{2.5}$ concentrations were 16.2 ± 8.4 μg/m^3 and 17.2 ± 5.0 μg/m^3, respectively with the highest concentration in winter (indoor: 18.8 ± 11.7μg/m^3; outdoor; 22.5 ± 5.0 μg/m^3). High $PM_{2.5}$ concentrations showed significant correlations with the aggravation of St George's Respiratory Questionnaire for COPD (SGRQ-C) and acute exacerbation, mainly in winter season. Lower socioeconomic patients were more susceptible to the increase of $PM_{2.5}$. Small airway resistance, the difference between resistance at 5 Hz and 20 Hz by the impulse oscillometry (R5-R20), also increased with $PM_{2.5}$ concentration.

Conclusion:

The ambient $PM_{2.5}$ concentration in individual COPD patients varied seasonally. The main clinical parameters affected by the higher levels of $PM_{2.5}$ were SGRQ-C, acute exacerbation and R5-R20, with the associations most prominent in winter.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease with significant worldwide morbidity and mortality [1]. Cigarette smoking is the most important risk factor, but around 30% of COPD patients are those who have never smoked [2-4]. Particulate matter (PM) is suggested as an important risk factor for development of COPD among various risk factors beyond smoking [5]. COPD exacerbations increase with PM exposure [6-9], and air pollutants can also aggravate symptoms, quality of life, and lung function in patients with COPD [10, 11]. Indeed, PM increases the risk of hospitalization, morbidity, mortality, and exacerbation in COPD [12].

Although numerous studies have reported the hazardous effects of PM in patients with COPD, previous studies have focused on the association between inhalable PM with aerodynamic diameters < 10 μm (PM_{10}) and COPD hospitalizations and mortality [13, 14]. Studies regarding PM with an aerodynamic diameter < 2.5 μm ($PM_{2.5}$) for COPD are relatively rare and have shown some contradictory results. One study in Hong Kong demonstrated a significant positive association between $PM_{2.5}$ and hospitalization [15]. However, another study conducted in Rome showed no association [16], whereas one in Birmingham even showed opposing results [17]. These studies were population-based and did not precisely measure PM concentrations at individual levels.

Korea, located in East Asia between China and the Pacific Ocean, has four distinct seasons. This geographic characteristic indicates that it experiences dynamic weather changes and air pollutant levels. Daily $PM_{2.5}$ level has a wide range, from 10 to 80 $\mu g/m^3$, with an annual mean of 29 $\mu g/m^3$. Such variations in weather and $PM_{2.5}$ levels provide an ideal condition to study the seasonal effect of $PM_{2.5}$ on health. This study thus aimed to prospectively evaluate individual exposure to $PM_{2.5}$ and the associations between $PM_{2.5}$ and clinical parameters in patients with COPD. We combined data from continuous $PM_{2.5}$ monitoring, various questionnaires, and regular hospital visits for one year in a COPD panel, and thereby assessed the impact of $PM_{2.5}$ on patients with COPD.

METHODS

Study Design and Participants

This was a prospective panel study conducted at four hospitals located across Korea. All patients with COPD were candidates for enrolment; the detailed inclusion and exclusion criteria are provided in the online supplement. We appraised the $PM_{2.5}$ concentrations and their association with clinical parameters for one year. Individual patients' ambient $PM_{2.5}$ concentrations and clinical parameters were evaluated. This study was approved by the Institutional Review Board (IRB) of each study site; Asan Medical Center (2019-0479), Gangneung Asan Hospital (2019-06-049), Ulsan University Hospital (2019-07-049), and Gachon University Gil Medical Center (GBirb2019-290). All participants received comprehensive information about the study and provided written informed consent. This study is registered at ClinicalTrials.gov (Registration No. NCT04020237). The detailed study protocols were described previously [18, 19].

Clinical Data Collection

A questionnaire survey was conducted to obtain further information on past medical history, current medication, residential environment, daily activities, protective behaviour against particulate matter, and socioeconomic status. The clinical outcomes were assessed trimonthly, including the COPD assessment test (CAT), modified MRC council dyspnoea scale, Saint George's respiratory questionnaire specific for COPD (SGRQ-C), and pulmonary function tests (PFT). Additionally, patients attending Asan Medical Center underwent serial impulse oscillometry (IOS).

Measurement of Particulate Matter concentration and Exposure

Indoor and outdoor $PM_{2.5}$ concentrations were monitored for individual patients, as previously described [18, 19]. A measurement device using a light-scattering sensor (CP-16-A5, Aircok, Seoul, Korea) was installed at pariticpants' residence, where they spend most of their times, to detect the indoor concentrations of $PM_{2.5}$. The Internet of Things (IoT) system was used to transfer the real-time data to a separate server throughout the study period. To quantify the background ambient air pollution level at the residence, data from the national database (http://www.airkorea.or.kr) were employed. The measurements from the observatories nearest to each patient's residential address were recorded as the outdoor concentration. $PM_{2.5}$ exposure level was assessed four times with a minivolume air sampler (Model KMS-4100, KEMIK Corp., Seongnam, Korea), two dust spectrometers (11-D, Grimm Technologies, and AM520, TSI, Shoreview, USA). Participants were instructed to carry a portable PM measuring device with Global Positioning System (GPS) (Airbeam2 from HabitatMap, Brooklyn, USA)

to measure the 24-hour exposure to $PM_{2.5}$. Participants also noted their whereabouts in a time-activity diary, and the GPS receiver also traced the patients' location [20]. $PM_{2.5} \geq 35$ μg/m^3 was defined as "severe" and $PM_{2.5} \geq 75$ μg/m^3 as "very severe" by the Ministry of Environment in Korea [21]. Consequently, the duration of $PM_{2.5}$ concentration above 35 μg/m^3 and 75 μg/m^3 for each participant was determined.

Statistical analysis

Data were analysed using Student's T-test, Mann-Whitney U test, Wilcoxon's signed-rank test, the χ^2 test, Fisher's exact test, or analysis of variance, as appropriate. The relationship between $PM_{2.5}$ concentrations and clinical outcomes was evaluated with Pearson's correlation coefficient and linear regression. Repeatedly measured data, were analysed with a linear mixed-effect model. A value of $P < 0.05$ was considered statistically significant (two-tailed). All statistical analyses were conducted using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 9; GraphPad Software, San Diego, CA).

RESULTS

Baseline Characteristics

A total of 126 patients were enrolled for this panel study. Among them, six withdrew consent, and 15 were lost to follow-up. Finally, 105 participants were included in the analysis. The mean age was 68.2 years, and 92.4% were male. Current or past smokers comprised 85.7% of patients. The mean post-bronchodilator forced expiratory volume in 1 second ($FEV_{1)}$ was 53.9% of the predicted value. The baseline CAT and SGRQ-C were 16.7 and 37.5. A history of acute exacerbation was present in 39.0% of patients (Table 1).

Table 1. Baseline characteristics of the study subjects

Baseline Characteristics	Total (n = 105)
Age, year	68.2 ± 7.2
Male sex	97 (92.4)
Smoking Status	
Current smoker	23 (21.9)
Former smoker	67 (63.8)
Never smoker	14 (13.3)
Smoking, pack-year	34.7 ± 23.0
Lung function	
Before bronchodilator	
FEV_1, litres	1.6 ± 0.5
FEV_1, % of predicted value	52.7 ± 16.2
FVC, litres	3.3 ± 0.8
FVC, % of predicted value	80.1 ± 14.6
After bronchodilator	
FEV_1, litres	1.6 ± 0.6
FEV_1, % of predicted value	53.9 ± 16.5
FVC, litres	3.4 ± 0.8
FVC, % of predicted value	80.6 ± 14.8
Inhaled medication	
None	1 (1.0)
LABA or LAMA	14 (13.3)
LABA + LAMA	23 (21.9)
LABA + ICS or LAMA + ICS	25 (23.8)
LABA + LAMA + ICS	42 (40.0)
History of acute exacerbation	41 (39.0)
SGRQ-C total score	37.5 ± 21.8
CAT score	16.7±8.2
MMRC	

Grade 0	4 (3.8)
Grade 1	42 (40.4)
Grade 2	25 (24.0)
Grade 3	25 (24.0)
Grade 4	8 (7.7)

Data are presented as mean ± standard deviation or number (%).

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; LABA, long-acting beta2-adrenergic agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; SGRQ-C St George's Respiratory Questionnaire specific for COPD; CAT, COPD assessment test; MMRC, Modified Medical Research Council

$PM_{2.5}$ Concentrations

During the study period, the mean indoor and outdoor $PM_{2.5}$ concentration were 16.2 μg/m^3 and 17.2 μg/m^3, respectively. Among four seasons, the concentrations were the highest in winter (18.8 μg/m^3 [indoor] vs. 22.6 μg/m^3 [outdoor], $P < 0.001$), and the lowest in fall (14.5 μg/m^3 [indoor] vs. 13.7 μg/m^3 [outdoor], $P = 0.068$, Figure 1A). The indoor/outdoor (I/O) ratios were 0.918 in spring, 1.112 in summer, 1.059 in fall and 0.837 in winter (Table 2). The mean duration of $PM_{2.5}$ concentration above 35 μg/m^3 was the longest in winter for both indoors (247.7 hours/mo) and outdoors (382.8 hours/mo, Figure 1B). Winter was again the season with the longest duration of $PM_{2.5}$ above 75 μg/m^3 (52.2 hours/mo [indoor], 15.5 hours/mo [outdoor], $P = 0.009$, Figure 1C).

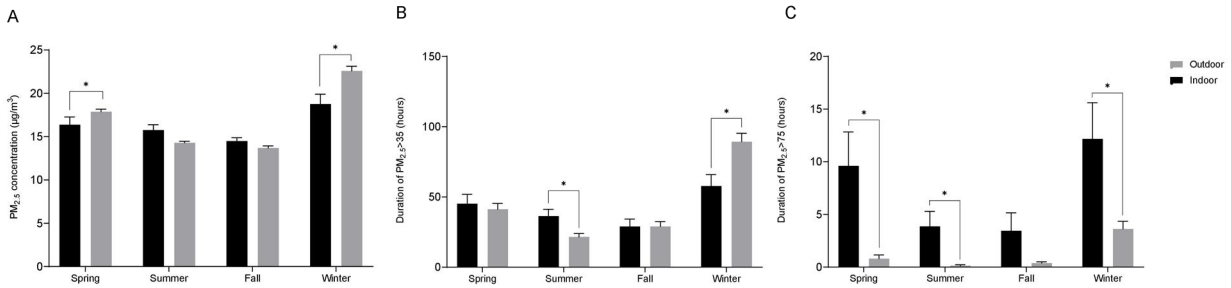
Smoking was a factor associated with $PM_{2.5}$ exposure. There were no significant differences between current smokers and not current smokers in mean indoor $PM_{2.5}$ (15.3 [current smokers] vs. 19.3 [not current smoker] hours, $P = 0.681$), and the duration of $PM_{2.5}$ at "severe" (1106.0 [current smokers] vs. 580.9 [not current smokers] hours, $P = 0.082$), however, duration of $PM_{2.5}$ at "very severe" (269.4 [current smokers] vs. 69.0 [not current smokers] hours, $P = 0.007$) levels were significantly longer among the smokers. (Figure 2). The construction year of the participants residence, presence of mold in house, frequency of cooking, types of heating system, opening windows, distance from the road and traffic quantity did not affect the observed $PM_{2.5}$ concentrations.

Table 2. Seasonal indoor/outdoor ratio of $PM_{2.5}$

	I/O ratio	*P* value
Season		<0.001
Spring	0.918	
Summer	1.112	
Fall	1.059	
Winter	0.837	
Location		0.048
Seoul	0.850	
Gangneung	1.046	
Inchon	1.249	
Ulsan	0.903	
Income		0.036
High	0.856	
Low	1.031	
Economic status		0.009
High	0.756	
Low	0.951	
Level of education		0.006
High	0.812	
Low	0.975	

I/O, indoor/outdoor ratio; $PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 um

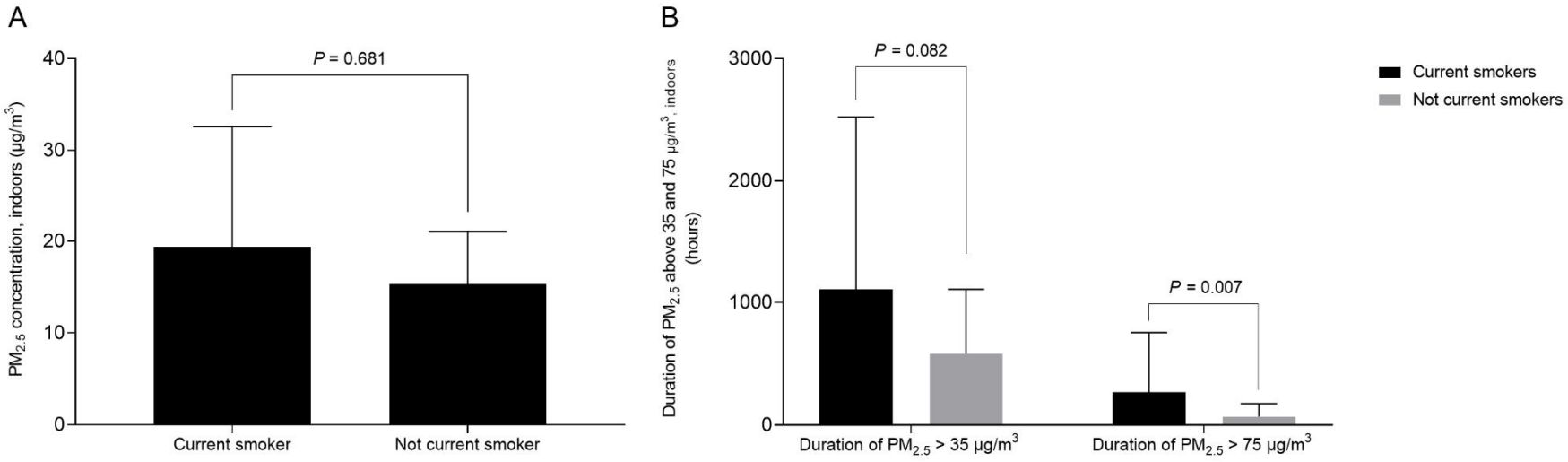
Figure 1. $PM_{2.5}$ concentrations in each season of the year



A Mean concentration of $PM_{2.5}$ B Duration of $PM_{2.5}$ concentration over 35 μg/m^3 C Duration of $PM_{2.5}$ concentration over 75 μg/m^3

Asterisk represents p value < 0.05. $PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 μm

Figure 2. Indoor $PM_{2.5}$ concentrations among current smokers and not current smokers



A Mean concentration of $PM_{2.5}$ B Duration of $PM_{2.5}$ concentration over 35 and 75 $\mu g/m^3$

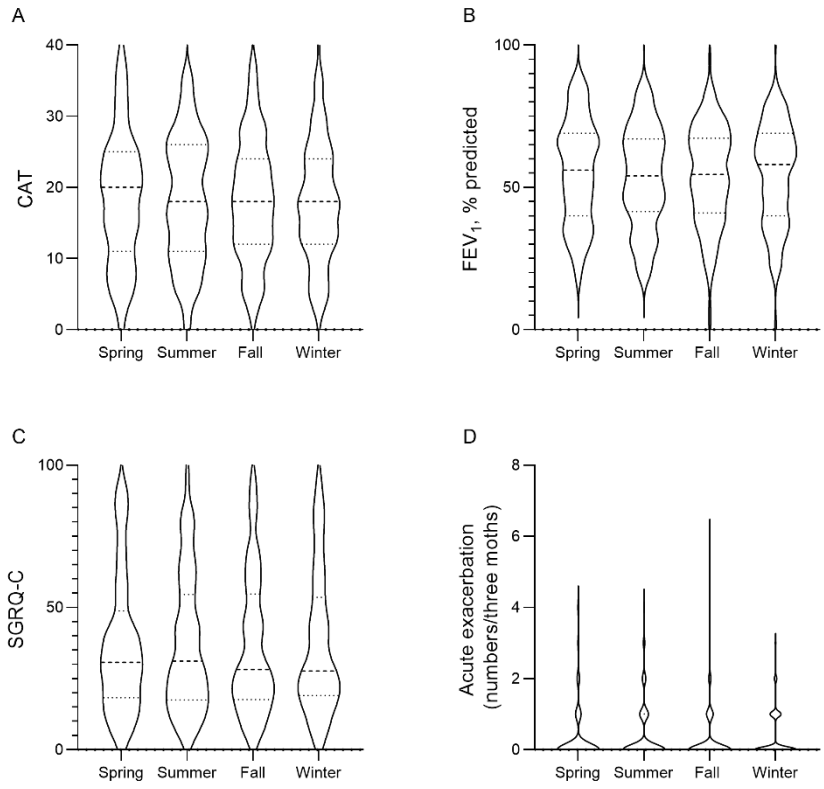
$PM_{2.5}$, particulate matter with aerodynamic size $\leq$ 2.5 μm

Clinical Outcomes

The clinical outcomes, including CAT, SGRQ-C, PFT, and acute exacerbations, did not show any significant differences among seasons. The median average CAT scores were 20.0, 18.0, 18.0, and 18.0 for spring, summer, fall, and winter, respectively, whereas the SGRQ-C scores were 30.7, 31.2, 28.2, and 27.6, respectively. The PFTs were performed on each visit to the clinic. The median FEV_1 (% of predicted value) after bronchodilator use were 56.0%, 54.0%, 54.5% and 58.0% in spring, summer, fall, and winter, respectively (Figure 3).

In this cohort, the factors associated with SGRQ-C and acute exacerbations were assessed with linear mixed effect model, with each patient and hospital as the random effects and age, sex, smoking status, FEV_1 and baseline value of either SGRQ-C or acute exacerbation as the fixed effects. The independent factors associated with SGRQ-C were, age (regression coefficient, 0.307; 95% confidence interval [CI], 0.123-95.77; $P = 0.015$) and baseline SGRQ-C (regression coefficient, 0.903; 95% CI, 0.048-95.655; $P < 0.001$). For acute exacerbation, age (regression coefficient, 0.010; 95% CI, 0.003-509.991; $P = 0.017$), baseline acute exacerbations (regression coefficient, 0.401; 95% CI, 0.033-487.401; $P < 0.001$) and FEV_1 (regression coefficient, -0.004; 95% CI, 0.002-508.708; $P = 0.029$) were significantly associated.

Figure 3. Clinical outcomes in each season of the year



The curves represent the probability density of the data at different values. The bold dotted line inside the curves shows the median, while paler dotted lines below and above the bold line are the first interquartile and the third interquartile range.

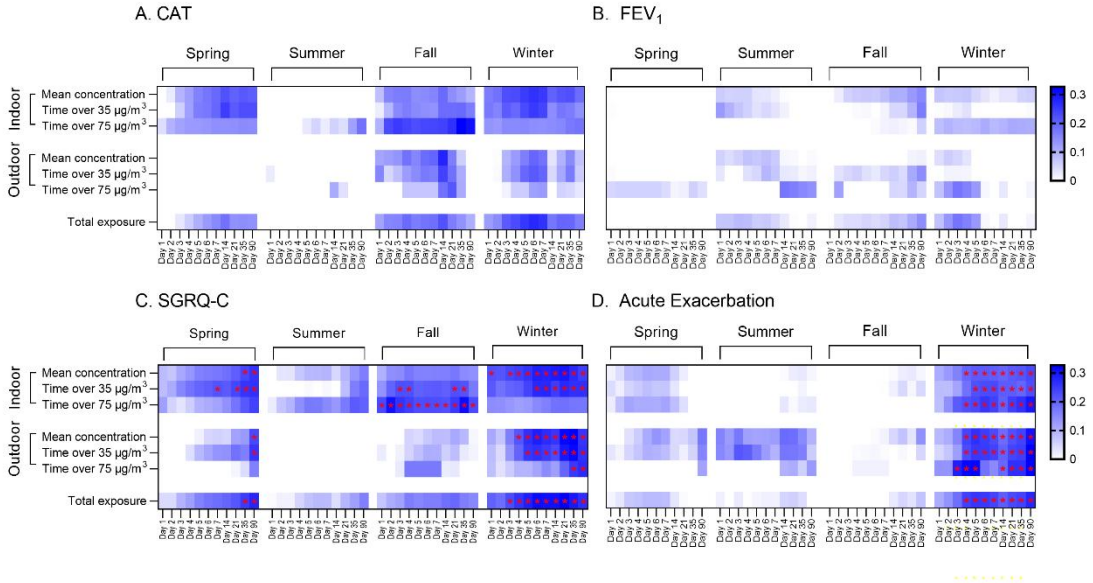
A The mean of CAT scores. B FEV_1, % prediction. C SGRQ-C scores. D Total number of acute exacerbations in the three months of each season

CAT, COPD assessment test; FEV_1, forced expiratory volume in 1 second; SGRQ-C, Saint George's Respiratory Questionnaire for COPD

Exposure to $PM_{2.5}$ and Clinical Outcomes

The correlations between $PM_{2.5}$ and clinical outcomes were assessed for each season. The significant relations of $PM_{2.5}$ with acute exacerbations were only present in winter. Indoor and outdoor mean concentration, duration of $PM_{2.5} \geq 35$ μg/m^3, 75 μg/m^3, and actual exposure concentration were all associated with acute exacerbations. The correlation coefficient was the highest in outdoor duration above 75 μg/m^3 within 90 days (r = 0.328), followed by outdoor duration above 35 μg/m^3 within 90 days (r = 0.327), outdoor mean concentration within 90 days (r = 0.305), indoor duration above 75μg/m^3 within 90 days (r = 0.298), and mean actual exposure concentration within 90 days (r = 0.279). Significant correlations with SGRC-C were noted in spring, fall, and winter. The correlations with the mean indoor concentration and mean actual exposure concentration were the strongest, with the Pearson correlation coefficient ranging from 0.197 to 0.263 and from 0.203 to 0.287, respectively. The CAT scores and FEV_1 did not show any significant correlations with $PM_{2.5}$ concentrations throughout the four seasons (Figure 4).

Figure 4. Correlation between the clinical outcomes and concentrations of PM2.5 during the days before the evaluation



A Mean CAT scores. B FEV1, % predicted. C SGRQ-C scores. D Number of acute exacerbations

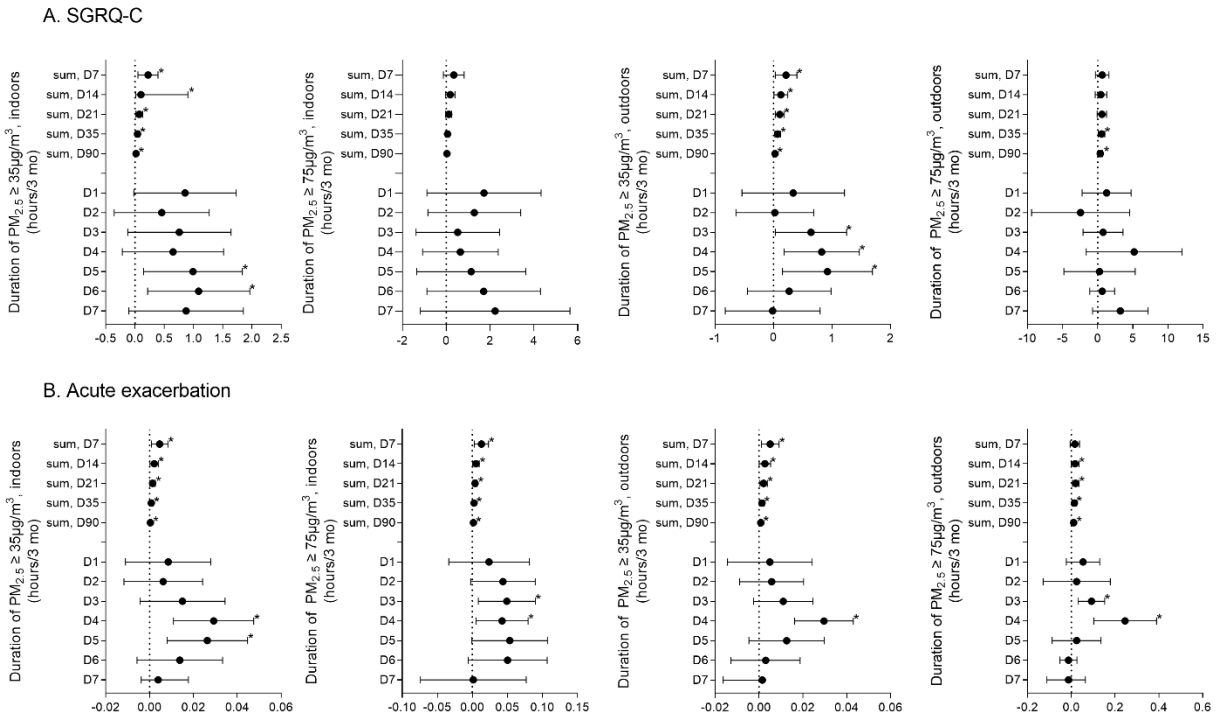
Asterisk represents *P* value < 0.05

$PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 μm; CAT, COPD assessment test; FEV_1, forced expiratory volume in 1 second; SGRQ-C, Saint George's Respiratory Questionnaire for COPD

The effects of $PM_{2.5}$ concentrations on SGRQ-C and acute exacerbations were further evaluated with multivariate logistic regression (Figure 5). In winter, SGRQ-C and acute exacerbation increased as the duration of $PM_{2.5}$ above 35 μg/m^3 or 75 μg/m^3 increased. Significant relationships with SGRQ-C were mainly found with duration above 35 μg/m^3. Meanwhile, an acute exacerbation was correlated with both indoor and outdoor duration above 35 μg/m^3 and 75 μg/m^3.

Moreover, multivariate linear regression model was fit to evaluate the relationship between $PM_{2.5}$ levels and acute exacerbations in winter. $PM_{2.5}$ levels were adjusted for age, previous exacerbations, smoking status and baseline FEV_1. The acute exacerbation was significantly associated indoor duration above 75 μg/m^3 over 90 days, outdoor duration above 35 μg/m^3 over 90 days, duration above 75 μg/m^3 over 21 days and over 90 days (Table 3)

Figure 5. Changes in SGRQ-C and number of acute exacerbations according to the duration of $PM_{2.5}$ during winter



The black circles represent changes in the SGRQ-C score or number of acute exacerbations per change in 1 hour. A $PM_{2.5}$ and SGRQ-C. B $PM_{2.5}$ and numbers of acute exacerbation in 3 months.Asterisk represents p value < 0.05

$PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 μm; SGRQ-C, Saint George's Respiratory Questionnaire for COPD

Table 3. Multivariate linear regression of acute exacerbation and $PM_{2.5}$ levels

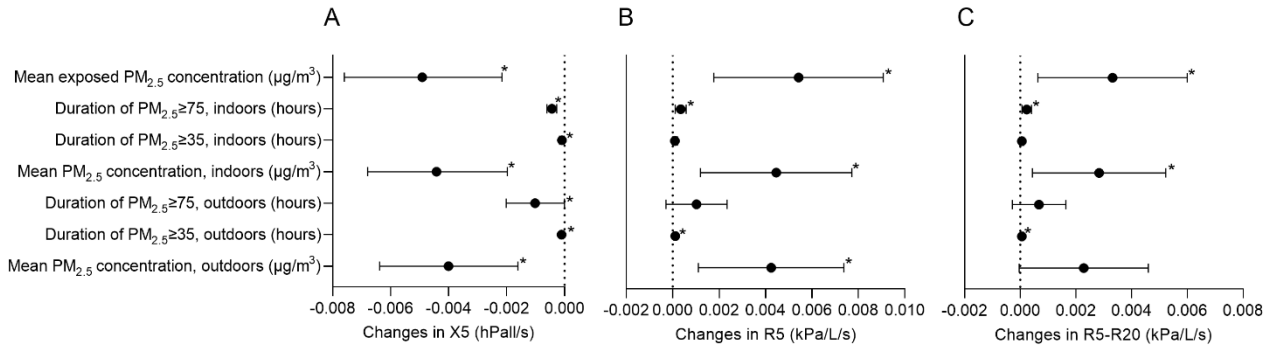
	Indoors			Outdoors		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Duration above 35 μg/m^3 over 90 days	1.000	0.999-1.001	0.101	1.001	1.000-1.001	0.033
Duration above 75 μg/m^3 over 21 days	1.002	0.999-1.005	0.168	1.007	1.000-1.013	0.037
Duration above 75 μg/m^3 over 90 days	1.001	1.000-1.002	0.036	1.015	1.001-1.029	0.039

CI, confidence interval

Relationship between $PM_{2.5}$ and IOS

The 44 patients enrolled in Asan Medical Center underwent IOS at each visit to the clinic. The relationship between $PM_{2.5}$ and IOS results was evaluated with a linear mixed-effect model. Changes in resistance at 5Hz (R5) – resistance at 20 Hz (R20) were positively associated with increases in the mean actual exposure concentration (*Δ*R5-R20: 0.003kPa/L/s, $P = 0.040$), outdoor above 35 μg/m^3 within 90 days prior to evaluation (*Δ*R5-R20: 0.00006kPa/L/s, $P = 0.046$), and indoor above 75 μg/m^3 in 90 days prior to evaluation (*Δ*R5-R20: 0.0002kPa/L/s, $P = 0.015$, Figure 6).

Figure 6. Changes in impulse oscillometry according to $PM_{2.5}$



A Changes in reactance at 5Hz. B Changes in resistance at 5 Hz. C Changes in the difference between airway resistance at 5 Hz and 20 Hz

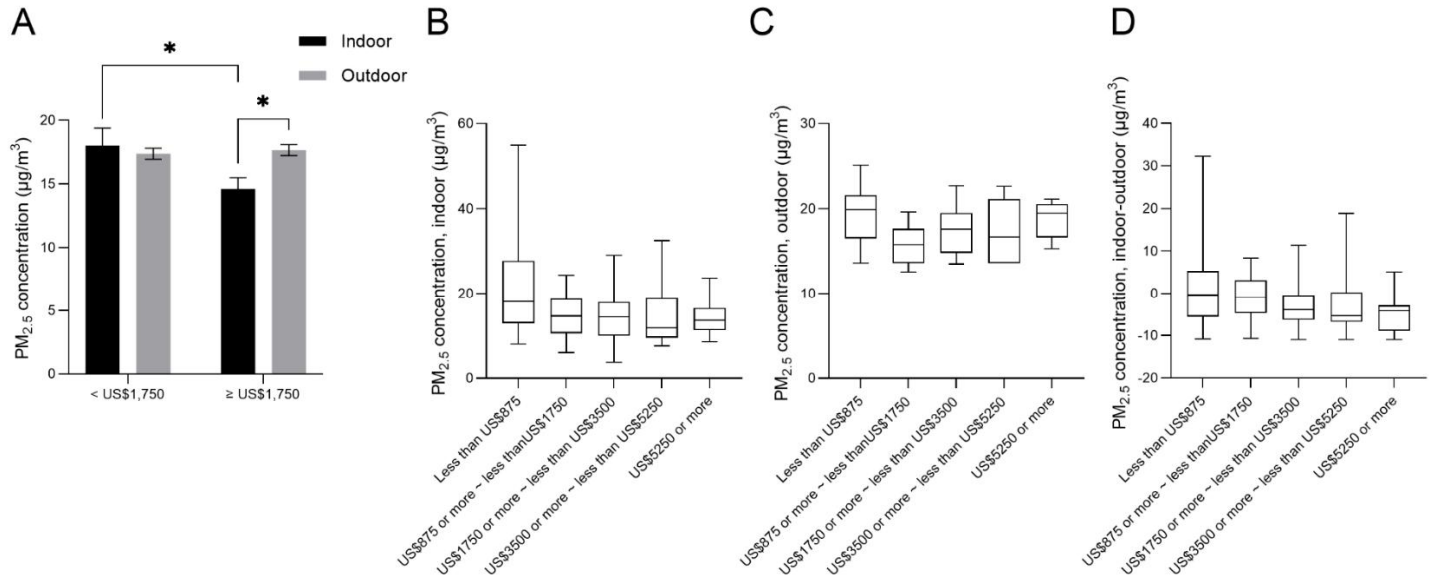
Asterisk represents p value < 0.05.

$PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 μm; X5, pulmonary reactance at 5 Hz; R5 airway resistance at 5Hz; R20 airway resistance at 20 Hz

Socioeconomic Factors, $PM_{2.5}$ and Clinical Outcomes

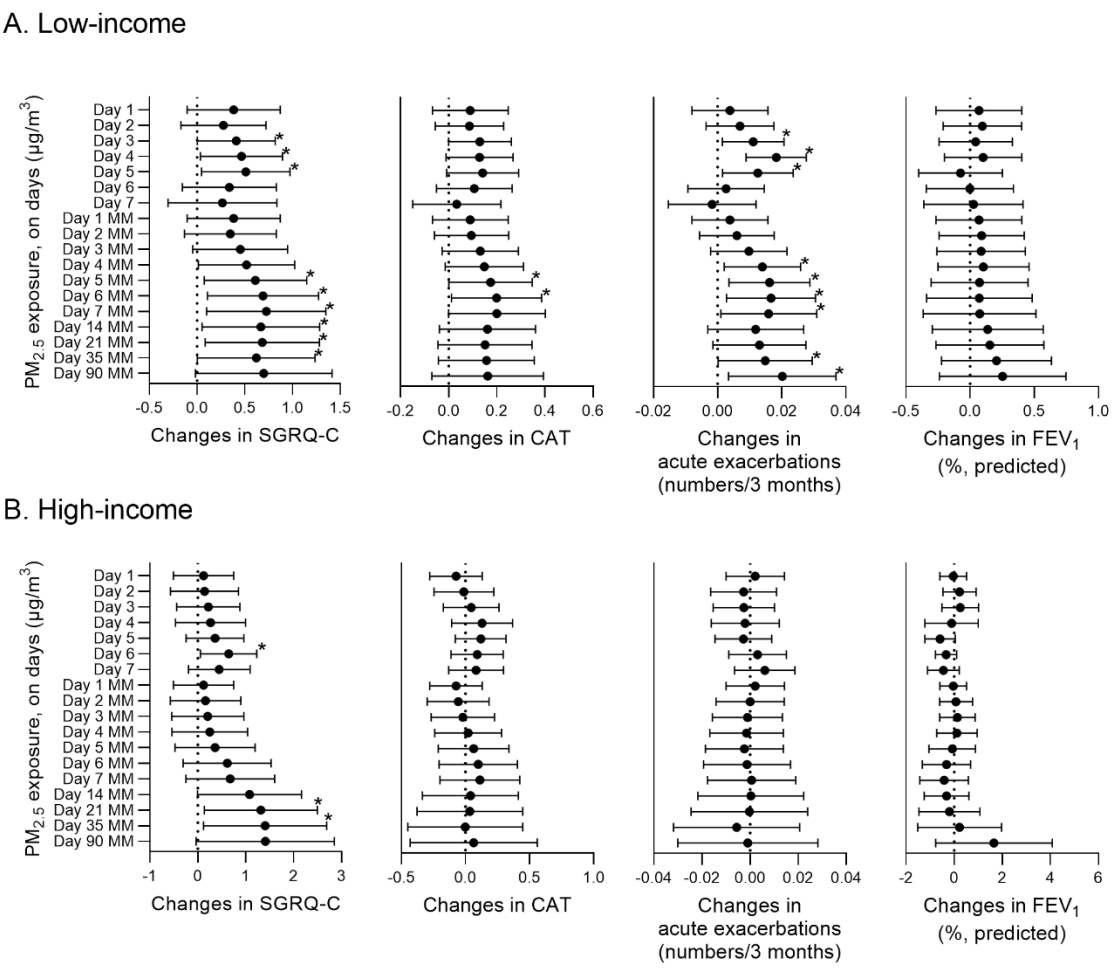
The associations between socioeconomic factors, monthly household income, economic status, and education level, and $PM_{2.5}$ concentrations were analysed. When the patients were allocated into the higher socioeconomic status group and lower socioeconomic status group, the higher groups invariably had significantly lower indoor $PM_{2.5}$ concentrations than outdoor concentration, whereas the lower group did not (Figure 7). In addition, during the winter season, changes in SGRQ-C and acute exacerbations were more often associated with $PM_{2.5}$ exposure levels in the groups belonging to the lower category of the socioeconomic status according to monthly household income, economic status, and education levels (Figure 8).

Figure 7. Indoor and outdoor $PM_{2.5}$ concentrations in relation to participants' income status



Participants were allocated to the low-income group if their monthly income was less than $1,750. A Mean individual ambient $PM_{2.5}$ concentrations of high-, and low- income group B Indoor $PM_{2.5}$ concentrations among different income groups C Outdoor $PM_{2.5}$ concentrations among different income groups D Difference from indoor $PM_{2.5}$ concentration to outdoor $PM_{2.5}$ concentration among different income groups Asterisk represents $P < 0.05$. $PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 μm

Figure 8. Subgroup analysis according to low-, and high-income groups in winter



A Changes of clinical parameters in low-income group B Changes in clinical parameters in high-income group

Asterisks represents p value < 0.05.

$PM_{2.5}$, particulate matter with aerodynamic size ≤ 2.5 μm

DISCUSSION

In this study, we followed COPD patients prospectively for one year, assessing their $PM_{2.5}$ exposure levels and clinical parameters. Patients were exposed to the highest ambient $PM_{2.5}$ concentration in winter, both indoors and outdoors. The changes in SGRQ-C and acute exacerbations were significantly associated with $PM_{2.5}$, especially in winter. There were significant positive relationships between the duration of $PM_{2.5} \geq 35$ μg/m^3 or 75 μg/m^3 and R5-R20. Socioeconomic factors also affected $PM_{2.5}$ concentrations. Groups with lower socioeconomic status were more vulnerable to $PM_{2.5}$ change, as SGRQ-C and acute exacerbations were more frequently associated with $PM_{2.5}$ concentration.

In our study, the ambient $PM_{2.5}$ concentration was the highest in winter, followed by spring, summer, and fall. Higher concentration in the colder season have also been repeatedly observed in other areas. A study from four regions in Switzerland found that the concentration was the highest in winter [22]. In a report from the US over 9 years, winter was also the highest season in terms of $PM_{2.5}$ concentration [23]. The important historical event that provided an insight on the environment, the great smog of London also occurred in December 1952. These seasonal characteristics of winter can be explained by atmospheric stagnation [24] combined with greater biomass burning [25] and combustion of fuel [24, 26] during the cold season, indicating that winter can be the most heavily affected season, making it the most difficult for susceptible patients with chronic respiratory disease. Additionally, in our study, the I/O ratio was <1 in winter and spring, whereas it was >1 in the other seasons. The factors known to affect the I/O ratio of $PM_{2.5}$ include temperature, indoor smoking, the structure of the building, and ventilation through windows [27].

In this study, we did not observe seasonal differences in health-related quality of life, lung function and acute exacerbation according to the seasons. However, significant correlations between $PM_{2.5}$ and clinical parameters were present with distinct patterns across the seasons. CAT and FEV_1 did not show any correlations with the levels of $PM_{2.5}$. SGRQ-C and acute exacerbations had significant correlations with $PM_{2.5}$ depending on seasons. Recently, Hansel et al. conducted randomized controlled trial exploring the effects of portable air cleaners on 116 patients with COPD. In the group that used the air cleaners, levels of $PM_{2.5}$, PM_{10} and NO_2 were lower than the placebo group, with subsequent better outcomes in terms of SGRQ and moderate exacerbations in per-protocol analysis [28]. Results from

both studies support that there are associations between $PM_{2.5}$ and health-related quality of life and exacerbations. The significant aggravation of SGRQ-C was noted as an ambient $PM_{2.5}$ increase in spring, fall and winter. Indoor concentrations were more frequently correlated with SGRQ-C, and correlations with outdoor concentrations were only observed in winter, suggesting the importance of indoor $PM_{2.5}$ control. Correlations between $PM_{2.5}$ and acute exacerbations were only present in winter. As winter had the highest concentration of $PM_{2.5}$, the correlation between $PM_{2.5}$ and the clinical outcome may be the most prominent in this season. Chinese group reviewed daily $PM_{2.5}$ concentrations and hospital records in Wuhan, China, and found stronger short-term effects of $PM_{2.5}$ on cardiorespiratory hospital admission during the cold season [29]. Similarly, a study from the United States investigated the effects of $PM_{2.5}$ on hospitalization for respiratory conditions in the from 1999 to 2005 and found the strongest effect of $PM_{2.5}$ during winter [30].

We found a significant positive association between the changes in SGRQ-C and acute exacerbations, and the duration of $PM_{2.5} \geq 35$ μg/m^3 and 75 μg/m^3. Our results suggest that an exposure to $PM_{2.5}$ above a certain concentration can provoke worsening of clinical outcomes in COPD. Furthermore, in our study, both short-term and relatively long-term effects, up to 90 days, were significant. In epidemiologic studies using home address information, long-term exposure to $PM_{2.5}$ has been associated with the development and progression of COPD [31, 32]. However, most studies investigating the relationship between COPD outcomes and exposure to $PM_{2.5}$ have focused on short-term exposures [29, 30]. In this context, this study provided a meaningful suggestion that $PM_{2.5}$ can have a gradual impact on COPD for at least up to 3 months, as confirmed by individual measurements of $PM_{2.5}$.

The IOS results in this study provided clues regarding the pathophysiology of $PM_{2.5}$ on COPD. We found significant positive relationships between changes in R5-R20 and $PM_{2.5}$ concentrations, although there were no associations between FEV_1 and $PM_{2.5}$. IOS is known to be more sensitive than FEV_1 at detecting small airway change [9, 33], and our results imply that $PM_{2.5}$ may aggravate small airways. The mechanism of damage due to $PM_{2.5}$ has been suggested in previous studies. Inhaled ultrafine particles can reach the small airways and remain there [34]. When human bronchial epithelial cells were exposed to $PM_{2.5}$, genes associated with the inflammatory response and extracellular IL-6 were upregulated [35], which has been associated with the development of asthma and COPD [36]. In a study that exposed mice to $PM_{2.5}$ for 48 weeks found increase in IL-6 in bronchoalveolar lavage fluid

and airway wall remodelling on microscopic examination [37]. These findings support the potential impact of $PM_{2.5}$ on small airway diseases, but further experiments are required to confirm whether this is the sole mechanism.

From the subgroup analysis, we found a trend toward better management of indoor $PM_{2.5}$ in high-socioeconomic groups. Participants in the low-socioeconomic groups failed to show reduced indoor $PM_{2.5}$ concentrations compared to outdoor $PM_{2.5}$, unlike the high-socioeconomic group. The $PM_{2.5}$ exposure levels were also more frequently associated with worse SGRQ-C or more frequent acute exacerbations in the low-socioeconomic group. Our findings are consistent with the results of previous population-based studies [38, 39]. A study based on area-level census data in Australia found that areas with greater socioeconomic disadvantage, a higher proportion of ethnic minorities and elderly were more heavily exposed to $PM_{2.5}$ [38]. Similarly, the analysis on the annual mean concentration of $PM_{2.5}$ of one million residential postcodes in England reported that total $PM_{2.5}$ was higher in areas of socioeconomic deprivation [39].

This study has several limitations. First, some clinical outcomes may not have reached statistical significance due to the relatively small number of patients. Meanwhile, we monitored $PM_{2.5}$ data continuously with the IoT system and collected detailed clinical and $PM_{2.5}$ exposure every 3 months, which could include about 400 measurement points in the analysis. Based on this individualized monitoring, we were able to probe into the diverse aspects of the relationship between $PM_{2.5}$ and COPD. Second, the study period encapsulated the COVID19 pandemic, which would have kept patients more at home, and their use of masks when outdoors would have decreased direct inhalation or contact with $PM_{2.5}$. These behavioural changes may have affected the clinical outcomes. Third, the attitude and behaviour towards $PM_{2.5}$ may be diverse depending on the country and culture, and the relation and impact of $PM_{2.5}$ may have some differences in detail according to the regions. However, we investigated the associations between $PM_{2.5}$ and clinical outcomes thoroughly and most of our results agree with those of previous reports of other countries. In addition, our previous report showed that the impact of lifestyle on indoor $PM_{2.5}$ such as air-filter use had findings consistent with previous reports from Western countries [40].

CONCLUSION

In this prospective panel study, we found a meaningful association between $PM_{2.5}$ and COPD. $PM_{2.5}$ showed dynamic seasonal changes in indoor and outdoor concentrations and $PM_{2.5}$ was associated with the deterioration of clinical outcomes, including SGRQ-C and acute exacerbation, mainly in winter when $PM_{2.5}$ was the highest. The small airway resistance markers by IOS were significantly affected by $PM_{2.5}$ changes, suggesting that $PM_{2.5}$ affects the small airways in COPD. Indoor $PM_{2.5}$ was more poorly controlled and the deterioration in SGRQ-C and acute exacerbation were more prominent in socioeconomically vulnerable patients in winter. Based on these findings, we can confirm that seasons and socioeconomic classes influence susceptibility to $PM_{2.5}$ exposure among COPD patients, which could be an important basis in the management of COPD.

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국문요약

초미세먼지는 만성폐쇄성 폐질환 환자의 발생과 입원, 사망과 연관성이 있는 것으로 알려져 있다. 하지만, 현재까지 초미세먼지와 만성폐쇄성 폐질환 사이의 관계를 분석한 연구들은 대규모 역학 자료를 바탕으로 이루어져 왔다. 초미세먼지농도와 실제 각 만성폐쇄성 폐질환 환자의 임상경과와의 연관성에 대한 연구는 아직 부족하다. 따라서 이 연구에서는 개별 만성폐쇄성 폐질환 환자 주변의 초미세먼지농도를 측정하면서 임상경과를 관찰하였다.

2019년부터 2020년까지 총 105명의 만성폐쇄성 폐질환 환자를 1년 동안 추적 관찰했다. 환자의 주거지에서 초미세먼지 농도를 측정하였으며, 환자 거주지 주변의 초미세먼지 농도 자료를 수집하였다.

만성폐쇄성 폐질환 환자 주변의 초미세 먼지 연간 평균 농도는 실내에서 16.2 μg/m^3이었으며 실외에서 17.2 g/m^3이었다. 계절별로는 겨울철에 가장 높은 농도를 보였다 (실내농도: 18.8 g/m^3, 실외농도: 22.5). 초미세먼지의 농도는 St George's Respiratory Questionnaire for COPD (SGRQ-C) 및 급성악화 발생과 유의미한 상관관계가 있는 것으로 나타났다. 특히 겨울철에서 상관관계가 두드러져 나타났다. 사회경제적으로 낮은 계층에 있는 환자들이 초미세먼지 농도 조절에 어려움을 겪고 있는 것으로 나타났으며, 이 환자들이 초미세먼지 농도에 더 많은 영향을 받고 있었다. 또한 초미세먼지 농도는 impulse osciollometry 값의 변화와 연관성이 있었는데 이는 초미세먼지가 소기도 저항에 영향을 미치는 것으로 볼 수 있다.

결론적으로 만성폐쇄성 폐질환 환자들이 계절별로 다른 초미세먼지 농도에 노출되었으며, 초미세먼지가 이들의 건강에 미치는 영향 역시 계절별로 다르게 나타났다. 가장 농도가 높으며 만성폐쇄성 폐질환 임상지표에 악영향을 보인 계절은 겨울이었다. 초미세먼지 농도와 가장 연관성이 깊은 임상지표는 SGRQ-C와 급성악화 빈도임을 확인할 수 있었다.