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ORIGINAL RESEARCH

Differences in the effects of Asian dust on pulmonary function between adult patients with asthma and those with asthma–chronic obstructive pulmonary disease overlap syndrome

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Background: Asian dust (AD) exposure exacerbates pulmonary dysfunction in patients with asthma. Asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS), characterized by coexisting symptoms of asthma and chronic obstructive pulmonary disease, is considered a separate disease entity. Previously, we investigated the effects of AD on pulmonary function in adult patients with asthma. Here, we present the findings of our further research on the differences in the effects of AD exposure on pulmonary function between patients with asthma alone and those with ACOS.

Methods: Between March and May 2012, we conducted a panel study wherein we monitored daily peak expiratory flow (PEF) values in 231 adult patients with asthma. These patients were divided into 190 patients with asthma alone and 41 patients with ACOS in this study. Daily AD particle levels were measured using light detection and ranging systems. Two heavy AD days (April 23 and 24) were determined according to the Japan Meteorological Agency definition. A linear mixed model was used to estimate the association between PEF and AD exposure.

Results: Increments in the interquartile range of AD particles (0.018 km^{-1}) led to PEF changes of −0.50 L/min (95% confidence interval, −0.98 to −0.02) in patients with asthma alone and −0.11 L/min (−0.11 to 0.85) in patients with ACOS. The PEF changes after exposure to heavy AD were −2.21 L/min (−4.28 to −0.15) in patients with asthma alone and −2.76 L/min (−6.86 to 1.35) in patients with ACOS. In patients with asthma alone, the highest decrease in PEF values was observed on the heavy AD day, with a subsequent gradual increase over time.

Conclusion: Our results suggest that the effects of AD exposure on pulmonary function differ between patients with asthma alone and ACOS, with the former exhibiting a greater likelihood of decreased pulmonary function after AD exposure.

Keywords: Asian dust, asthma, asthma–chronic obstructive pulmonary disease overlap syndrome, peak expiratory flow, pulmonary function

Introduction

Asian dust (AD), called also yellow dust, originates in East Asia deserts and is the second largest sand dust emission in the world.[1] Therefore, AD transports a large amount of particulate matter to East Asia. Over the last decade, AD has become a serious problem because it contains several industrial pollutants emitted by the rapidly expanding industries and the increasing number of cars on the roads in East Asia.[2–7] Numerous studies have shown that ADS is associated with hospital visits and admission, cardiovascular onset and mortality, and cerebrovascular and pulmonary disease. AD aggravates mortality and increases the requirement for emergency treatment and hospitalization for

cardiovascular disease and pulmonary disease.[8–11] In particular, AD exposure is associated with exacerbation of asthma. In children with asthma, South Korean studies showed that AD is associated with an increase in acute respiratory symptoms and changes in the peak expiratory flow (PEF).[12,13] AD can also increase the risk of hospital visits for exacerbation of asthma.[14] Both Kanatani et al[15] and Ueda et al[16] reported that AD was associated with an increased risk of hospitalization in children with asthma. Our previous studies also demonstrated that AD could aggravate lower respiratory symptoms and pulmonary function in adult patients with asthma.[17,18] The interesting aspect is that the effects of AD on asthma occur over several days after the exposure.

In the spectrum of chronic airway diseases, asthma and chronic obstructive pulmonary disease (COPD) are common and highly prevalent in the general population. Although both asthma and COPD exhibit variable degrees of airway inflammation, airway obstruction, and airway hyperresponsiveness,[19,20] both are different and independent diseases. Several studies have demonstrated differences in inflammatory cell recruitment, mediator production, and therapeutic responses between asthma and COPD.[21,22] Airway flow limitation is progressive and mostly irreversible in COPD, whereas it is typically intermittent and reversible in asthma.[23] Of late, there is evidence of an increasing number of patients with some coexisting manifestations of asthma and COPD, a condition known as asthma–COPD overlap syndrome (ACOS).[24,25] ACOS primarily affects individuals with long-standing asthma, particularly current or former smokers.[24] Patients with ACOS exhibit high mortality rates, poorer health-related quality of life, and higher exacerbation rates compared to patients with asthma or COPD alone.[24–28] Therefore, we speculate that the effects of AD exposure on pulmonary function differ between patients with asthma and those with ACOS, although few studies have actually investigated these differences.

In 2012, we conducted a panel study to investigate the effects of AD exposure on pulmonary function in adult patients with asthma in western Japan and demonstrated that heavy exposure to AD particles was significantly associated with decreased pulmonary function in this population.[18] In this study, we performed subgroup analyses to investigate differences in the effects of AD exposure on pulmonary function between patients with asthma alone and those with ACOS among the 2012 cohort.

Methods

Study design

In our panel study conducted from March to May 2012, we measured daily PEF values in 231 patients with asthma aged >18 years.[18] The patients resided in Yonago City, Matsue City, Sakaiminato City, Yasugi City, or Saihaku Town, all of which are located within 25 km of Tottori University Hospital in Yonago City, western Japan. On the basis of the Global Initiative for Asthma (GINA)[29] criteria, the patients were diagnosed with asthma if they presented with a history of intermittent wheezing and exhibited airway hyperresponsiveness to methacholine or exhibited reversible airflow limitations (12% and 200 mL variability in the forced expiratory volume in 1 second [FEV_1]). If patients had other disorders or dementia, they were exempt from recruitment into the study. When patients were unable to measure pulmonary function and understand the methods of measuring PEF with a peak flow meter (Mini-Wright, Harlow, England, American Thoracic Society scale), they were excluded from recruitment. To study differences in the effects of AD on pulmonary function between adult patients with asthma alone and those with ACOS, we divided the 231 patients into 190 patients with asthma alone and 41 patients with ACOS in the present study. ACOS was clinically diagnosed on the basis of the GINA[29] and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (2014),[30] which dedicated a joint chapter to ACOS to underline the clinical importance of this syndrome. Briefly, patients with a previous diagnosis of asthma, a smoking history of at least 10 pack-years, persistent airflow limitations (postbronchodilator FEV_1/forced vital capacity [FVC] ratio, <0.7), and respiratory symptoms were diagnosed with ACOS. Diagnoses of allergic rhinitis and chronic sinusitis were made by an otolaryngologist. This study was approved by the institutional ethics committee (Ethics Committee of Tottori University, Approval Number 1656), and all patients provided written informed consent for participation.

Monitoring of air pollutants and definition of a heavy AD day

Concentrations of nitrogen dioxide (NO_2), ozone, particulate matter smaller than 2.5 μm ($PM_{2.5}$), sulfur dioxide (SO_2), and suspended particulate matter (SPM) are monitored at many locations in Japan by the Japanese Ministry of the Environment. For this analysis, we collected data for SPM, SO_2, and NO_2 from the Yonago observatory and collected data for $PM_{2.5}$ from the Matsue observatory.

Light detection and ranging (LIDAR) systems can measure particulate matter as nonspherical airborne particles, which are equivalent to sand dust particles, and spherical airborne particles, which are equal to air pollution aerosols, by simultaneously illuminating a target with two laser beams of different wavelengths and analyzing the reflected light.[31,32]

These systems can also measure the amount of AD particles transported for long distances from East Asia to Japan because they are simultaneously applied within <1 km above the ground, and measurements are continuously obtained from various locations in Japan, South Korea, People's Republic of China, Mongolia, and Thailand.[31,32] Accordingly, the levels of nonspherical particles measured by LIDAR measurements are equivalent to the quantity of AD particles. The levels of spherical particles, which consist of organic aerosols, inorganic sulfates, and nitrates, are measured at 15 minutes intervals, and daily particle levels are determined from the median value of 96 measurements collected over a 24 hours period from midnight of one day to midnight of the following day.[31,32] For this analysis, LIDAR data for spherical and nonspherical particles were obtained from the Matsue observatory. Values measured at 120–150 m above the ground, which is the minimum altitude required by LIDAR systems to measure nonspherical and spherical particles, were used. LIDAR measurements do not distinguish particles by size and lack defined criteria for heavy AD. Therefore, a heavy AD day was determined according to the information provided by the Japan Meteorological Agency, which was based on a criterion of visibility <10 km due to sand dust arising from the East Asian deserts combined with meteorological satellite data.

Recording of daily PEF values and asthma control test (ACT) scores

From February to May 2012, morning PEF levels were recorded daily by all patients using a peak flow meter. February was used as the trial period. PEF values were measured three times in the morning, before the inhalation of corticosteroids or β_2-agonists or consumption of oral drugs. Each patient recorded the best of the three obtained values. Scores for the Japanese version of the Asthma Control Test (ACT-J) were recorded at the end of each month.[33]

Statistical analysis

The Mann–Whitney *U*-test and the chi-squared test were used for comparisons between patients with asthma alone and those with ACOS. For evaluating the effects of exposure to AD, AD particle levels detected by LIDAR, and daily average SPM and $PM_{2.5}$ levels, we adopted linear mixed models, which can appropriately account for correlations among repeated measurements within a subject.[34,35] The daily (24 hours) average levels of air pollutants (SO_2, NO_2, and ozone) and meteorological variables such as daily temperature, humidity, and atmospheric pressure were used. The linear mixed models included a random intercept for subjects for accounting the correlations of repeated measurements and the following covariates were adjusted: individual characteristics (age, sex, smoking, treatment steps, and ACT scores); meteorological variables such as daily temperature, humidity, and atmospheric pressure; and the exposures of interest. Estimates are presented as the absolute change in the PEF value per interquartile range (IQR) change in exposure, with 95% confidence intervals (CIs). We also performed significance tests for assessing the differences in effects between the two strata. To investigate differences in the effects of heavy exposure to AD on PEF according to patient characteristics, we conducted stratified analyses according to the presence/absence of rhinosinusitis and $\%FEV_1$ values. The effects of heavy exposure to AD and the postexposure effects on PEF from 0 (heavy AD day) to 5 days after the heavy exposure were also evaluated, considering the effects of dust exposure on PEF can persist for up to 3 days.[12] For the statistical analyses, we used SPSS software (Japanese version 22.0 for Windows; SPSS Japan Inc., Tokyo, Japan) and R version 3.0.3 (R Foundation for Statistical Computing, Vienna, Austria); especially for the analyses of linear mixed models, we adopted the lme4 package of R. All quoted *P*-values are two sided and the significance levels were set at 0.05.

Results

Patient characteristics

The PEF values of all 231 registered patients were recorded daily for >95% of the study period from March to May. The characteristics of patients with asthma alone and those with ACOS are listed in Table 1. A treatment step, maintenance treatment, and pulmonary function tests were performed, and ACT scores were obtained on February 2012. There were significant differences between the two groups with regard to age, sex, smoking status, FEV_1, $\%FEV_1$, FEV_1/FVC, the presence of rhinosinusitis, treatment steps, inhaled corticosteroid dose, and long-acting β_2-agonist use. Patients with ACOS were older than those with asthma alone and exhibited poorer pulmonary function and a lower prevalence of rhinosinusitis.

Levels of AD particles, SPM, and $PM_{2.5}$

The daily levels of AD particles, SPM, and $PM_{2.5}$ are shown in Figure 1. Two heavy AD days were identified by the Japan Meteorological Agency, one on April 23 and another on April 24.

PEF changes

The results of changes in PEF per IQR increase in the levels of AD particles, SPM, and $PM_{2.5}$ after adjustment for

Table 1 Characteristics of patients

Variable	All patients	Patients with asthma alone	Patients with ACOS	*P*-value
Number, n	231	190	41	
Age (years)	61.9±16.1	59.6±16.3	71.9±10.5	<0.001
Sex; male/female, n	93/138	55/135	38/3	<0.001
Smoking status				<0.001
Never, n (%)	156 (67.5)	156 (82.1)	0 (0)	
Former, n (%)	62 (26.8)	29 (15.2)	33 (80.5)	
Pack-year history	46.2±31.3	33.5±22.3	41.2±22.8	
Current, n (%)	13 (5.7)	5 (2.7)	8 (19.5)	
Pack-year history	25.7±16.7	21.1±11.9	51.2±32.7	
ACT score				
Mean	22.4±3.3	22.7±3.2	23.2±2.3	0.314
25, n (%)	88 (38.1)	70 (36.8)	18 (43.9)	
20–24, n (%)	100 (43.3)	81 (42.6)	19 (46.3)	
20>, n (%)	43 (18.6)	39 (20.6)	4 (9.8)	
Pulmonary function				
FVC (L)	3.01±0.74	3.12±0.97	3.35±0.68	0.155
FEV_1 (L)	2.16±0.66	2.39±0.84	1.95±0.61	0.002
$\%FEV_1$ (%)	98.0±23.5	105.7±24.7	85.7±23.2	<0.001
FEV_1/FVC	0.72±0.12	0.76±0.10	0.57±0.11	<0.001
Rhinosinusitis, n (%)	94 (40.7%)	89 (46.8)	5 (12.2)	<0.001
Treatment step				0.022
Step 1, n (%)	3 (1.3)	3 (1.6)	0 (0)	
Step 2, n (%)	31 (13.4)	29 (15.3)	2 (4.9)	
Step 3, n (%)	46 (19.9)	40 (21.1)	6 (14.6)	
Step 4, n (%)	141 (61.0)	112 (58.9)	29 (70.7)	
Step 5, n (%)	10 (4.3)	9 (3.1)	1 (9.8)	
ICS dose				0.019
Low dose, n (%)	51 (22.1)	49 (25.8)	2 (4.9)	
Medium dose, n (%)	118 (51.1)	93 (48.9)	25 (61.0)	
High dose, n (%)	59 (27.8)	48 (25.3)	11 (26.8)	
LABA use, n (%)	171 (74.0)	130 (68.4)	41 (100)	0.023
Leukotriene receptor antagonist use, n (%)	106 (45.9)	96 (50.5)	13 (31.7)	0.152
Theophylline use, n (%)	23 (10.0)	14 (7.4)	9 (22.0)	0.094
Oral corticosteroid use, n (%)	8 (3.5)	7 (3.7)	1 (2.4)	0.694
Omalizumab use, n (%)	3 (1.3)	2 (1.1)	1 (2.4)	0.479

Note: Data are expressed as mean ± SD or the number (%).
Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; ACT, asthma control test; FEV_1, forced expiratory volume in 1 second; $\%FEV_1$, percentage of predicted FEV_1; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonists; SD, standard deviation.

individual characteristics and meteorological variables are listed in Table 2. Patients with asthma alone exhibited a significant association between PEF values and exposure to AD particles and spherical particles, but not between PEF values and exposure to SPM and $PM_{2.5}$. However, no significant associations were observed for the overall cohort and for patients with ACOS. In addition, there were no significant effect modifications between the two strata (*P*=0.474, 0.265, and 0.527 for AD particles, SPM, and $PM_{2.5}$, respectively). Associations between PEF values and heavy exposure to AD are listed in Table 3. There was a significant negative association between heavy exposure to AD and PEF levels in all patients and patients with asthma alone. To facilitate evaluation of the effects of heavy AD exposure on PEF values in all patients and patients with asthma alone, the changes are shown from 0 (heavy AD day; lag 0 days) to 5 days after heavy exposure (lag 0–5 days). The highest decrease was observed on day 0, and the values gradually improved with time. There were also no observed significant effect modifications in these evaluations (eg, *P*=0.781 for lag 0 day).

Table 4 presents the association between daily PEF levels after heavy AD exposure and patient characteristics; a significant association was observed for patients with rhinosinusitis.

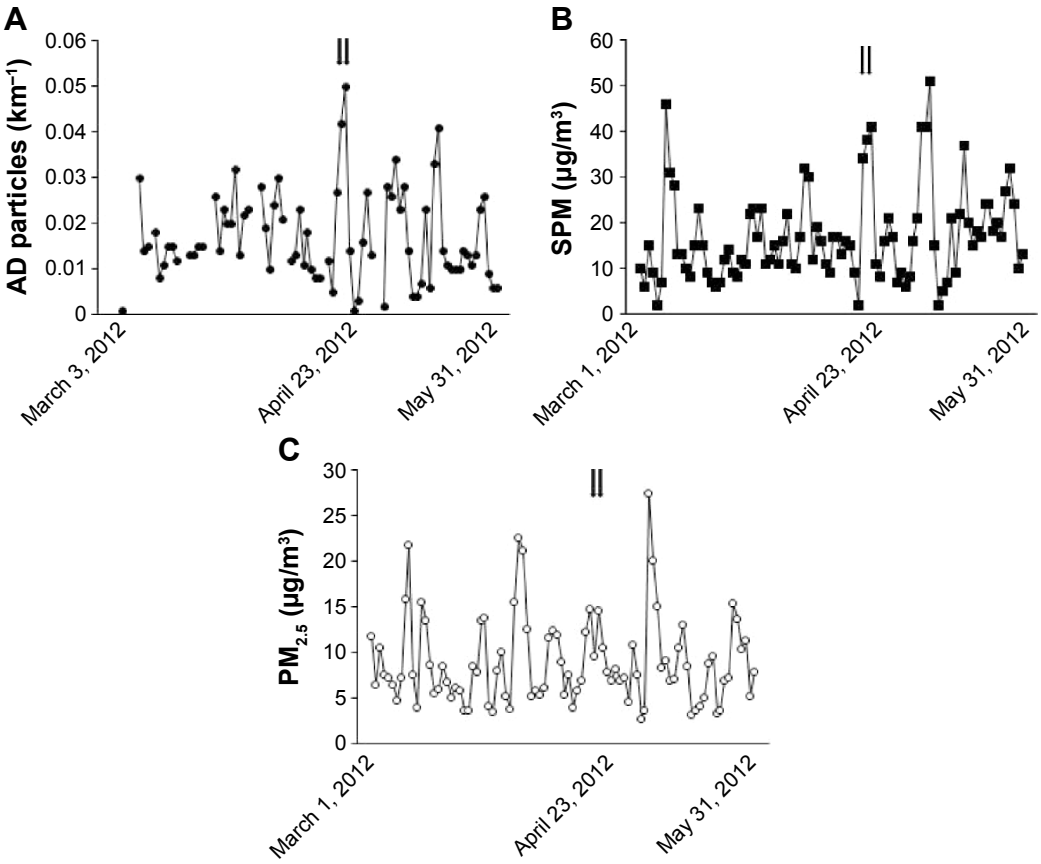

Figure 1 Daily levels of particles (**A**), SPM (**B**), and $PM_{2.5}$ (**C**).
Notes: Data pertaining to AD levels are missing for 16 days from March to May 2012, including 10 days in March, 4 in April, and 2 in May. Two heavy AD days, determined according to the definition recommended by the Japan Meteorological Agency, can be observed, one on April 23 and another on April 24. The arrows indicate the heavy AD days.
Abbreviations: AD, Asian dust; SPM, suspended particulate matter; $PM_{2.5}$, particulate matter smaller than 2.5 μm in diameter.

Table 2 Associations of PEF with exposure to AD particles, spherical particles, SPM, and $PM_{2.5}$ according to linear mixed models after adjustment for individual characteristics and meteorological variables

Exposure	IQR	Change in PEF (L/min)	95% CI	*P*-value
All patients (n=231)				
AD particles	0.018 km^{-1}	−0.43	−0.86 to 0.01	0.051
SPM	11.8 μg/m^3	−0.17	−0.53 to 0.21	0.397
$PM_{2.5}$	6.9 μg/m^3	0.03	−0.35 to 0.42	0.865
Patients with asthma alone (n=190)				
AD particles	0.018 km^{-1}	−0.50	−0.98 to −0.02	0.042
SPM	11.8 μg/m^3	−0.25	−0.66 to 0.15	0.227
$PM_{2.5}$	6.9 μg/m^3	−0.02	−0.45 to 0.41	0.927
Patients with ACOS (n=41)				
AD particles	0.018 km^{-1}	−0.11	−1.06 to 0.85	0.825
SPM	11.8 μg/m^3	0.27	−0.54 to 1.10	0.508
$PM_{2.5}$	6.9 μg/m^3	0.29	−0.57 to 1.15	0.513

Notes: The linear mixed models included a random intercept for subjects in the analysis, individual characteristics, meteorological variables, gaseous air pollutants (nitrogen dioxide, ozone, and sulfur dioxide), and other parameters related to AD particles, SPM, and $PM_{2.5}$ that deviated from the evaluation.
Abbreviations: AD, Asian dust; ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; CI, confidence interval; IQR, interquartile range; PEF, peak expiratory flow; $PM_{2.5}$, particulate matter smaller than 2.5 μm in diameter; SPM, suspended particle matter.

Discussion

Some studies have shown that exposure to AD is associated with an increased risk of hospitalization and deterioration of pulmonary function and respiratory symptoms in patients with asthma.[12–18] ACOS was recently defined as a new entity.[29,30] Patients with ACOS are more likely to develop frequent and severe respiratory exacerbations compared to patients with asthma alone.[36] However, few studies have demonstrated differences in the effects of AD exposure on pulmonary function between patients with asthma alone and those with ACOS. To the best of our knowledge, this study is the first to compare patients with asthma alone and those with ACOS and specifically link asthma with a greater decrease in pulmonary function after AD exposure. The study also demonstrated that PEF values were associated with daily levels of AD particles, but not with daily levels of SPM and $PM_{2.5}$, in patients with asthma alone.

ACOS primarily affects elderly patients, particularly smokers, with a long-term history of asthma.[24–30] We avoided bias caused by patient characteristics such as age, sex, and

Table 3 Association between PEF changes and exposure to heavy AD

Lag time (days)	Change in PEF (L/min)	95% CI	*P*-value
All patients (n=231)			
Lag 0	−2.31	−4.16 to −0.46	0.014
Lag 0–1	−1.88	−3.41 to −0.35	0.016
Lag 0–2	−1.77	−3.12 to −0.42	0.010
Lag 0–3	−1.69	−2.92 to −0.46	0.007
Lag 0–4	−1.32	−2.46 to −0.19	0.023
Lag 0–5	−1.11	−2.17 to −0.05	0.041
Patients with asthma alone (n=190)			
Lag 0	−2.11	−4.28 to −0.15	0.036
Lag 0–1	−1.94	−3.64 to −0.23	0.026
Lag 0–2	−1.80	−3.31 to −0.30	0.019
Lag 0–3	−1.79	−3.17 to −0.43	0.010
Lag 0–4	−1.45	−2.72 to −0.19	0.025
Lag 0–5	−1.31	−2.50 to −0.13	0.030
Patients with ACOS (n=41)			
Lag 0	−2.76	−6.86 to 1.35	0.188
Lag 0–1	−1.66	−5.07 to 1.76	0.342
Lag 0–2	−1.64	−4.63 to 1.36	0.285
Lag 0–3	−1.20	−3.92 to 1.53	0.389
Lag 0–4	−0.73	−3.25 to 1.79	0.570
Lag 0–5	−0.18	−2.53 to 2.18	0.883

Notes: Calculated for an interquartile change in heavy AD exposure and adjusted for individual characteristics and meteorological variables. A heavy AD day was determined according to the information provided by the Japan Meteorological Agency.

Abbreviations: ACOS, asthma–chronic obstructive pulmonary disease overlap syndrome; AD, Asian dust; CI, confidence interval; PEF, peak expiratory flow.

smoking history by including a random intercept for subjects in the analysis. In addition, we treated treatment steps and ACT scores as fixed effects. After eliminating this important bias, we found different effects of AD exposure in patients with asthma alone and those with ACOS. The pathophysiology of ACOS is mostly unknown. However, smokers with asthma develop pathological changes similar to those observed in COPD.[37,38] Differences in the pathophysiology of asthma and ACOS may have led to the differences observed in our study.

Table 4 Association between daily PEF values after exposure to heavy AD and patient characteristics

Variable	Change in PEF (L/min)	95% CI	*P*-value
Patients with rhinosinusitis (n=88)	−3.25	−5.51 to −0.98	0.005
Patients without rhinosinusitis (n=143)	−0.77	−3.93 to 2.38	0.632
$\%FEV_1$ ≥80% (n=181)	−1.60	−3.78 to 0.57	0.149
$\%FEV_1$ <80% (n=50)	−0.38	−5.06 to 4.30	0.873

Notes: Estimates and 95% confidence intervals for changes in PEF (L/min) in all patients after adjustment for meteorological variables. A heavy AD day was determined according to the definition recommended by the Japan Meteorological Agency.

Abbreviations: AD, Asian dust; CI, confidence interval; $\%FEV_1$, percentage of predicted forced expiratory volume in 1 second; PEF, peak expiratory flow.

Nasal dysfunction due to concomitant rhinosinusitis in patients with asthma is a risk factor for deterioration.[39] In this study, the prevalence of rhinosinusitis was significantly different between patients with asthma alone and those with ACOS, and subgroup analyses revealed that an attenuation of pulmonary function was more likely after heavy AD exposure in patients with rhinosinusitis. Thus, this could have been one of the reasons for the different effects of AD exposure in patients with asthma alone and those with ACOS. Asthma is known to be associated with a high prevalence of rhinosinusitis,[39] while ACOS has shown no clear association thus far. Studies on nose–lung interactions and functional complementarity in ACOS may be important to further clarify the effects of AD exposure on pulmonary function in patients with asthma alone and those with ACOS.

The size distribution of AD particles is primarily 3.3–4.7 μm, with the diameter ranging from 0.5 to 10 μm.[40] Therefore, most studies have investigated the effects of AD exposure on health according to the levels of particulate matter measuring <10 μm in diameter (PM_{10}) and $PM_{2.5}$. In Japan, SPM is defined by the National Air Quality Standard as any particle with a diameter of <10 μm with a 100% cutoff,[41] whereas PM_{10} is defined as any particle measuring less than 10 μm in diameter with a 50% cutoff. However, SPM, PM_{10}, and $PM_{2.5}$ are a complex mixture of various solid and liquid particles. Therefore, AD particles cannot be clearly distinguished from other particulate matter on the basis of SPM, PM_{10}, and $PM_{2.5}$. To overcome this problem, Japanese studies started using LIDAR data.[15,16] In this study, patients with asthma alone showed a significant association between PEF values and daily levels of AD particles and AD particle levels on heavy exposure days as measured by LIDAR systems.

Understandably, pulmonary function was poorer in the overall cohort than in patients with asthma alone. When patients were classified into two groups according to $\%FEV_1$ in subgroup analyses, both ≥80% and <80% groups showed no association between PEF values and heavy AD exposure. These results suggest that poor pulmonary function was not a risk factor for a decrease in PEF values after AD exposure.

This study has some limitations. First, there may be a potential for selection bias because the included patients regularly attended respiratory clinics and were treated by chest physicians. In particular, untreated patients with ACOS may also exhibit an aggravation of pulmonary dysfunction

after AD exposure. Therefore, our results may have underestimated the effects of AD exposure on pulmonary function. Second, we were unable to estimate the amount of exposure to SPM, $PM_{2.5}$, and AD particles for each individual. Finally, we did not assess the amount of pollen, which may affect pulmonary function in patients with concomitant rhinosinusitis.

Conclusion

Within the limitations of the study, the results suggest that the effects of AD exposure on pulmonary function differ between patients with asthma alone and those with ACOS, with the former exhibiting a greater likelihood of a decrease in pulmonary function after exposure to AD. Patients with asthma alone may show a greater decrease in pulmonary function by exposure to AD than those with ACOS.

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Author contributions

MW, JK, HS, ES, and HK conceived the study. MW, HN, and HS participated in the design. MW, JK, YU, MM, HY, HT, KK, TK, and TT collected the data. MW and HN performed the analysis. MW, HN, JK, and HS drafted the manuscript. All authors had full access to all study data and take full responsibility for the data integrity and accuracy of analysis. All authors further contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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