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Effects of air pollution on moderate and severe asthma exacerbations

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ABSTRACT

Background: Few studies have evaluated the impact of air pollution levels on the severity of exacerbations. Thus, we compared the relative risks posed by air pollutant levels on moderate and severe exacerbations.

Methods: Exacerbation episodes of 618 from 143 adult asthmatics were retrospectively collected between 2005 and 2015 in a tertiary hospital of Korea. Air pollution GPS data for the location closest to each patient's home were obtained from the national ambient monitoring station. The relative impacts of air pollutants on asthma exacerbations were evaluated via a time-trend controlled symmetrical, bidirectional, case-crossover design using conditional logistic regression models on the day of the exacerbation (T-0) and up to 3 days before the exacerbation (T-1–T-3).

Results: Overall asthma exacerbation were associated with O₃ levels in summer and winter (OR: 1.012[1.003–1.02] and 1.009[1.003–1.016]), SO₂ levels in spring and summer (OR: 1.009[1–1.018] and 1.02[1.006–1.035]) and NO₂ levels in winter (OR: 1.007[1.003–1.011]). Analyses of the temporal relationship between O₃ concentrations and exacerbations demonstrated that 63.2% of episodes in the summer occurred when the O₃ concentrations on T-1 were significantly higher than those on control days, while 51% of exacerbation episodes in the winter occurred. Severe and moderate exacerbations were similarly associated with O₃ levels in winter (OR: 1.012 [1.003–1.02] vs. 1.01 [0.999–1.021], $p > 0.05$) and in summer (OR: 1.006 [1.002–1.009] vs. 1.009 [1.003–1.016], $p > 0.05$).

Conclusions: Asthma exacerbations may be associated with the seasonal elevation of O₃, SO₂ and NO₂ levels in summer and winter with the similar relative risk between moderate and severe exacerbations.

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Introduction

Asthma is a chronic inflammatory airway disease characterized by airflow limitation and airway hyper-responsiveness (1,2). Asthma exacerbations are particularly important in asthma management because morbidity and mortality are closely related to the frequency and severity of these exacerbations (3,4). Thus, the identification of causal factors is essential for preventive control of exacerbations. Numerous environmental and social factors, including exposure to sensitized allergens, viral infection, heavy exercise, smoking, obesity and medications can induce exacerbations (5,6). Ambient air pollutants are also considered important triggers, and this is supported by studies published over the last several decades (7–10).

Recently, a meta-analysis of 22 studies among 208 publications performed between 2000 and 2016 showed significant associations of major pollutants including O₃, NO₂, CO, and PM_{2.5} with moderate and severe exacerbations of asthma requiring emergency department visits (EDVs) and/or hospitalization (11).

In the *post hoc* analysis, the exacerbations were significantly associated with NO₂, SO₂, and PM_{2.5} in childhood pediatric subgroup. Asthma exacerbations can be classified as mild, moderate, and severe, with the latter two generally requiring an EDV and likely hospitalization (12). According to several meta-analysis (6,13–15), these pollutants in the atmosphere are associated with higher incidence, prevalence, hospitalizations, or worsening of symptoms of childhood

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asthma. Regarding the short-term effects of air pollutants in terms of exacerbations or worsening of symptoms, three studies have found an association with PM, NO₂, SO₂, carbon monoxide (CO) and O₃ (13,16,17). However, a small number of studies have been performed on adult asthmatics. In fact, increased air pollution is associated with EDVs of chronic obstructive pulmonary disease (COPD) patients and elderly asthmatics and exacerbations of adult refractory asthma (RA) in patients who were relatively resistant to conventional asthma medications (18,19). The findings from previous studies have shown definite seasonal changes in relation to asthma symptoms in children and adults. In particular, a number of studies have reported that the numbers of children and adolescents who present at emergency departments (EDs) and are hospitalized because of asthma exacerbations dramatically increase during fall in several places of the world (20–24). In a study done in Korea (25), where the present study was performed, a total of 41,128 subjects who were presented at the EDs from 2007 to 2012 were analyzed using the National Emergency Department Information System records from 117 EDs that comprised all of the patients with asthma. The monthly numbers of EDVs for asthma varied according to the season, with high peaks during fall, which was from September to November, and low levels in summer, which was from June to August. In addition, important differences in the seasonal patterns of EDVs for asthma are evident in children and adolescents of Korea (25) as has been demonstrated in asthmatics of several countries (20–24). Because air pollutants induces airway inflammation (26) and more intense inflammation of asthmatic airways is accompanied by severe exacerbation (27), we hypothesized that severe exacerbation is associated with air pollutants more than moderate exacerbation.

Thus, we explored the associations of levels of ambient air pollutions with moderate and severe exacerbations of asthma.

Materials and methods

Study population

We retrospectively analyzed the clinical data of adult asthmatics contained within an asthma registry database at Soonchunhyang University (28) and evaluated 618 exacerbation episodes of 143 asthmatics, who experienced one or more exacerbations between 2005 and 2015. They were regularly followed at the interval of 2–3 months with measurement of FEV1. Whenever episodes of increased dyspnea, wheezing, or cough were developed during the follow-up period, they

visited out-patient clinics or ER department, and exacerbation was defined as described previously by ATS/ERS statement (29). Although 200 asthmatics were included at initial study but 57 asthmatics having no address information or incorrect address information were excluded. Asthma was diagnosed by physicians according to the following criteria: the presence of reversible airway obstruction (variation in peak expiratory flow rate >20% over a 4-week follow-up period or short-acting bronchodilator-induced increase in forced expiratory volume in 1 sec [FEV1] >12%/200 ml), the presence of airway hyperreactivity (methacholine PC20 <10 mg/ml) or improvement of FEV1 >20% after 2–4 weeks of treatment with inhaled or systemic corticosteroids. At the baseline visit, demographic information including age at enrollment, sex, asthma onset age, asthma duration, body mass index (BMI), and smoking amount were collected. Current smokers and ex-smokers with >10 pack years were excluded from the study. All subjects underwent a standardized assessment, including complete blood cell and differential counts, measurement of immunoglobulin (IgE) levels, chest posteroanterior radiography, spirometry, and skin prick tests for 24 common inhalant allergens including dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*), cat fur, dog fur, cockroaches, grass pollens, tree pollens, ragweed pollens, and *Aspergillus* species (Bencard Co; Brentford, UK). Asthma duration was the time elapsed between the age of onset and the age of recruitment. Exacerbations were defined by episodes of increased dyspnea, wheezing, or cough, as described previously (30). Moderate exacerbations were defined as exacerbations that recovered only by increasing the dose of inhaled corticosteroids and/or by addition of bronchodilators or leukotriene receptor antagonists. Severe exacerbations were defined as exacerbations that recovered only by addition of systemic corticosteroids (>0.5 mg/kg of prednisolone for >3 days), being events requiring urgent action to prevent a serious outcome such as hospitalization or death (30). Exclusion criteria were ex-smokers who smoked more than 10 pack-years or current smokers for adjusting smoking factor, and COPD, vocal cord dysfunction, obstructive sleep-apnea, Churg-Strauss syndrome, and cardiac dysfunction. The protocol was approved by the Ethics Committees of Soonchunhyang Bucheon Hospital (SCHBC_2014_07_028).

Meteorological and air pollution data

Meteorological global positioning system (GPS) data (<https://data.kma.go.kr/>) including mean daily

temperature, daily temperature range, relative humidity and air pressure were obtained from the national monitoring site closest to the address of each patient. Air pollution GPS data (<http://www.airkorea.or.kr/index>) for the location closest to each patient's home were also obtained from the national ambient monitoring station. In the analysis, we included daily average (24 h) levels of particulate matters with an aerodynamic diameter of <10 microns (PM₁₀), CO, sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and ozone (O₃).

Statistical analysis

The relative impacts of ambient air pollution levels and meteorological conditions on asthma exacerbations were evaluated via a time-trend controlled symmetrical, bidirectional, case-crossover design using conditional logistic regression models. Symmetrical and bidirectional control selection was performed to control time trends (31): four control days were selected at fixed intervals of 7 and 14 days before and after the day of each episode. Meteorological conditions and air pollution concentrations on the day (T-0) of exacerbation and up to 3 days before (T-1–T-3) were compared with the equivalent averaged data on selected control days using the Wilcoxon rank-sum test. Odds ratios (ORs) for exposure to pollutants were calculated to estimate the risk of exacerbations according to a unit increase in air pollution and meteorological condition levels (32). We analyzed the data by two stages: first, we performed the conditional logistic regression models for all exacerbations. Secondly, exacerbations were divided into moderate and severe exacerbation, and then the conditional logistic regression models was applied in each group. The data were also stratified into four seasons: spring

(March–May), summer (June–August), autumn (September–November), and winter (December to February) to control for seasonal variation. We conducted multiple sensitivity analyses: First, several single-pollutant models were constructed for all exacerbation episodes. Secondly, correlation analysis of the relationship between meteorological conditions and air pollution levels was performed using Spearman's rank correlation coefficient, followed by analysis using multi-pollutant models controlling for all variables. All analyses were performed using SPSS software (ver. 22.0; SPSS Inc., Chicago, IL, USA). The effect of ambient air pollution levels and meteorological conditions on the risk of exacerbations were estimated as ORs per 10 ppb change for SO₂, CO, O₃, NO₂ and 10 °C change for temperature along with their 95% confidence intervals (CIs).

Results

Clinical characteristics of the study population

Among the 618 episodes of exacerbations, 331 were moderate and 287 were severe. Regarding the severe exacerbation episodes, 40 subjects collectively had 81 hospital admissions and four subjects had 14 EDVs. Clinical and demographic characteristics of the patients are summarized in Table 1. The median asthma duration was significantly longer ($p=0.01$) and the FEV₁ measured during the exacerbations was significantly lower ($p<0.0001$) in the severe versus moderate exacerbations group (Table 1). There was no difference in any clinical variables among the seasons (Table S1). Among the study subjects, 96% lived in urban areas and 11% lives in rural areas. More than 90% of the study subjects (129 among 143) lived

Table 1. Clinical characteristics of study population.

Variables	Total	Moderate exacerbation	Severe exacerbation	<i>p</i> -value
Number	143 subjects	331 events	287 events	
- Subject by season*	89/75/90/71	49/48/50/41	40/27/40/30	0.649
- Case by season*	170/155/163/130 (618)	90/87/87/67	80/68/76/63	0.8841
Age (years)	56 (18–84)	56 (18–84)	57 (18–84)	0.834
Asthma-onset age (years)	41 (1–74)	38 (1–74)	40 (5–74)	0.625
Asthma duration (years)	6.4 (1.1–17.1)	5.7 (1.1–12.4)	6.6 (1.2–17.1)	0.01
Female (%)	121 (84.6%)	84/102 (82.3%)	67/78 (85.8%)	0.292
BMI (kg/m ²)	23.8 (16.0–35.0)	24.0 (16.0–33.8)	24.1 (16.0–35.0)	0.112
Non-smoker/ex-smoker#	129/14 (9.8%)	90/12 (11.7%)	72/6 (7.7%)	0.733
Smoking amount (pack-years)	0 (0–9)	0 (0–9)	0 (0–6)	0.14
Positive rate of skin prick test (%)	71 (49.6%)	55/102 (53.9%)	38/78 (48.7%)	0.931
Total IgE (IU/l)	154 (0–3564)	145 (0–3564)	127 (0–3182)	0.152
Initial FEV ₁ (% predicted)	68 (24–116)	67 (24–108)	66 (24–116)	0.425
FEV ₁ (% predicted) _personal best	69 (34–118)	69 (34–106)	67 (37–118)	0.484
FEV ₁ (% predicted) _Exacerbation	61 (21–118)	66 (23–106)	57 (21–118)	0.0001

*Spring, summer, autumn and winter.

#Ex-smoker with <10 pack-years.

Data are presented as median (ranges) if not mentioned otherwise.

Table 2. Air pollution levels and meteorological conditions at the day of exacerbation and at the average of control days.

Variables	Spring	Summer	Autumn	Winter
<i>Day of exacerbation with the episode</i>				
<i>Air pollutant</i>				
SO ₂ (10 ppb)	64.6 (10–161.7)	41.7 (6.5–156.1)	47.6 (11.3–207.5)	70 (12.5–261.7)
CO (10 ppb)	60 (19.16–177.08)	50.65 (10–120.5)	59.1 (11.91–203.33)	74.16 (20.41–198.75)
O ₃ (10 ppb)	240.9 (41.3–720)	209.8 (35–522.5)	130.4 (16.3–487.1)	116.7 (19.5–360.8)
NO ₂ (10 ppb)	387.4 (46.3–999.2)	289.6 (42.3–957)	338.3 (56.3–840)	346.7 (34.1–727.9)
PM10 (μg/m ³)	65 (9.58–825.83)	39.48 (5.08–109.79)	45.21 (8.52–199.29)	58.33 (11.19–171.46)
<i>Meteorological factor</i>				
Temperature avg. (°C)	11.6 (–2.9–25.2)	23.35 (16.4–29.3)	14.8 (–4.2–25.5)	0.1 (–13.7–11.7)
Daily range (°C)	9.3 (2.1–21.3)	7.1 (1.8–15.6)	8.4 (2.1–18.2)	7.6 (2.8–19.1)
Relative humidity (%)	59.8 (25.6–96.6)	78.2 (37.3–100)	66.1 (32.9–93)	60.6 (25.9–96.8)
Air pressure (hPa)	1006.4 (952.6–1025.1)	999.8 (952.2–1009.2)	1010.1 (967.9–1028.6)	1015.3 (954.7–1031.3)
<i>Control days (7 and 14 days before and after each episode)</i>				
<i>Air pollutant</i>				
SO ₂ (10 ppb)	59.8 (4.3–2230)	40.8 (38–167.4)	49.2 (10–204.6)	75 (13–249.2)
CO (10 ppb)	59.16 (10–225.41)	48.69 (10–150)	60.83 (10–207)	75.21 (10–310.83)
O ₃ (10 ppb)	239.6 (46.3–658.8)	205.1 (20–692.1)	140 (20–534.6)	106.2 (10.9–751.3)
NO ₂ (10 ppb)	351.7 (17.1–1160.7)	277.1 (12–907.1)	342.1 (20.8–986.3)	353.7 (26.9–900.8)
PM10 (μg/m ³)	63.4 (4.04–766.42)	43.77 (7–155.77)	46.83 (5.95–241.42)	57.69 (12.63–182.75)
<i>Meteorological factor</i>				
Temperature avg. (°C)	10.9 (–2.8–25.2)	23.8 (15.6–29.3)	15.3 (–4.2–26.3)	0.2 (–12.9–11.5)
Daily range (°C)	9.3 (2–22.2)	6.85 (1.4–14.8)	8.5 (2–19.3)	7.2 (2.3–20.2)
Relative humidity (%)	58.55 (24.3–98.9)	78.45 (35–99.3)	66.4 (27.4–95.4)	60.75 (25.9–97.6)
Air pressure (hPa)	1006.1 (955.3–1026)	998.8 (952.7–1013.8)	1009.4 (962.2–1028.9)	1015.3 (963.8–1032.3)

in Kyunggi, Inchoen and Seoul provinces (A total area of 11,835 km²).

Association of exacerbations with the levels of air pollutants and meteorological conditions

Air pollutants and meteorological conditions were measured at 62 and 7 monitoring sites, respectively. Median distances were 2.2 km (range: 0.01–24.71) and 12.4 km (range: 2.62–23.27) far from the home address of each study subject, respectively. Air pollution data were missing for 43 days. Levels of air pollutants and meteorological conditions on the day of exacerbation (T-0) were not significantly different from those on the control days (Table 2). The same result showed in the severe and moderate exacerbation model (Table S2). In the conditional logistic regression model, variables having a significant relationship with the independent variable in correlation analysis ($|r| > 0.3$) were considered as confounders and controlled as previously described (33). The correlation coefficients between the levels of air pollutants and meteorological factors are shown in Table S3. The exacerbations in multi-pollutant models were significantly associated with O₃ levels in summer and winter (OR: 1.012, 95% confidence interval [CI]: 1.003–1.02 and 1.009 [95% CI: 1.003–1.016] on T-1), SO₂ levels in spring and summer (OR: 1.009 [95% CI: 1–1.018] and 1.02 [95% CI: 1.006–1.035] on T-1) and NO₂ levels in winter (OR: 1.007 [95% CI: 1.003–1.011] on T-1). (Table 3, Figure 1). We performed an additional analysis of the temporal relationship between O₃

concentrations and the onset time of exacerbations to determine a direct relationship between O₃ exposure and asthma exacerbation episode. In the summer, 63.2% of episodes (81 out of 128) occurred when the O₃ concentration on T-1 was significantly higher than that on control days, while only 51% of exacerbation episodes (54 out of 107) occurred in the winter (Figure 2). The frequency was marginally increased in the summer compared to that in the winter ($p = 0.064$ calculated using Chi-square test). In addition, O₃ levels (10 ppb) were significantly higher in the summer than the winter on T-1 (median [ranges] 245.8[36.3–621.3] vs. 111.7[19.2–426.7], $p < 0.0001$) and on control days (204.0[44.8–395.1 ppb] and 112.5[32.5–357.1], $p < 0.0001$).

Comparison of O₃, NO₂ and SO₂ levels between severe and moderate exacerbations

Both severe and moderate exacerbations were significantly associated with O₃ levels to the similar extent in winter (OR: 1.012 [95% CI: 1.003–1.02] vs. 1.01 [95% CI: 0.999–1.021], $p > 0.05$ on T-1, respectively) and in summer (OR: 1.006 [95% CI: 1.002–1.009] vs. 1.009 [95% CI: 1.003–1.016], $p > 0.05$ on T-1, respectively) (Table S4 and Figure 1). There was no difference between the severe and the moderate exacerbation with respect to NO₂ levels in winter (1.007 [1.001–1.013] on T-1 vs. 1.008 [1.001–1.015] on T-2, $p > 0.05$) and SO₂ levels in summer (1.023 [1.001–1.046] vs. 1.017 [0.996–1.039] on T-1, $p > 0.05$). (Figure 1, Table S4). In the single-pollutant model as

Table 3. Odds ratio and 95% confidence interval (CI) for the relation of ambient air pollution and exacerbation by unit increase of air pollutants.

Season (sample/case)	T=0	T=1	T=2	T=3	Adjusted variable
Spring (89/150)	SO ₂ (10 ppb)	1.004 (0.995–1.013)	1.009 (1.000–1.018)*	0.997 (0.988–1.007)	CO, NO ₂ , PM10
	CO (10 ppb)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	SO ₂ , NO ₂
	O ₃ (10 ppb)	1.000 (0.997–1.002)	1.002 (1.000–1.005)	0.999 (0.997–1.002)	CO, NO ₂
	NO ₂ (10 ppb)	1.000 (0.998–1.003)	0.999 (0.996–1.001)	0.999 (0.996–1.001)	SO ₂ , CO, O ₃ , PM10
	PM10 (µg/m ³)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.001)	SO ₂ , CO, NO ₂
	Temperature avg. (10 °C)	1.000 (0.994–1.005)	0.999 (0.994–1.004)	0.994 (0.989–1.000)	Humidity, Atmos_press
	Daily range (10 °C)	0.997 (0.990–1.004)	0.999 (0.989–1.002)	0.997 (0.990–1.004)	Humidity
	Relative humidity (%)	1.000 (0.986–1.014)	0.990 (0.977–1.005)	1.000 (0.985–1.015)	Temp_diff
	Air pressure (hPa)	1.020 (0.985–1.057)	1.028 (0.992–1.066)	1.006 (0.972–1.041)	Temp_avg
	SO ₂ (10 ppb)	1.011 (0.997–1.025)	1.020 (1.006–1.035)*	1.016 (1.003–1.029)	NO ₂ , PM10
	CO (10 ppb)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	NO ₂ , PM10
	O ₃ (10 ppb)	1.001 (0.999–1.003)	1.012 (1.003–1.020)*	1.009 (1.003–1.016)*	Humidity
	NO ₂ (10 ppb)	1.000 (0.997–1.002)	0.994 (0.991–0.997)	0.998 (0.996–1.000)	SO ₂ , CO, PM10
Summer (62/132)	PM10 (µg/m ³)	0.999 (0.998–1.001)	0.999 (0.998–1.001)	1.000 (0.998–1.001)	SO ₂ , CO, NO ₂
	Temperature avg. (10 °C)	0.991 (0.981–1.001)	0.988 (0.978–0.998)	0.995 (0.986–1.005)	O ₃ , humidity
	Daily range (10 °C)	0.997 (0.985–1.009)	0.986 (0.975–0.997)	0.991 (0.979–1.003)	O ₃ , Temp_diff
	Relative humidity (%)	0.994 (0.966–1.022)	0.992 (0.965–1.019)	0.984 (0.959–1.010)	
	Air pressure (hPa)	1.034 (0.989–1.082)	0.996 (0.986–1.006)	1.017 (0.974–1.063)	
	SO ₂ (10 ppb)	0.996 (0.985–1.008)	0.988 (0.975–1.001)	0.993 (0.982–1.005)	CO, NO ₂ , PM10
	CO (10 ppb)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	SO ₂ , O ₃ , NO ₂ , PM10
	O ₃ (10 ppb)	0.996 (0.992–1.000)	1.000 (0.996–1.004)	0.997 (0.994–1.001)	CO, NO ₂
	NO ₂ (10 ppb)	0.998 (0.996–1.001)	0.998 (0.996–1.001)	0.999 (0.997–1.001)	SO ₂ , O ₃ , CO, PM10
	PM10 (µg/m ³)	1.000 (0.999–1.001)	1.000 (0.999–1.001)	1.000 (0.999–1.001)	SO ₂ , CO, NO ₂
	Temperature avg. (10 °C)	0.997 (0.991–1.002)	0.999 (0.993–1.004)	1.000 (0.994–1.006)	humidity, Atmos_press
	Daily range (10 °C)	0.997 (0.989–1.005)	0.993 (0.985–1.002)	0.997 (0.989–1.006)	Humidity
	Relative humidity (%)	1.006 (0.987–1.027)	0.995 (0.975–1.015)	1.004 (0.984–1.025)	Temp_avg, Temp_diff
Autumn (72/143)	Air pressure (hPa)	0.989 (0.943–1.038)	0.982 (0.936–1.03)	0.980 (0.935–1.028)	Temp_avg
	SO ₂ (10 ppb)	0.998 (0.988–1.009)	0.999 (0.987–1.011)	0.997 (0.987–1.007)	O ₃ , CO, NO ₂ , PM10
	CO (10 ppb)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	1.000 (1.000–1.000)	SO ₂ , O ₃ , NO ₂ , PM10, Temp_avg
	O ₃ (10 ppb)	1.006 (0.999–1.012)	1.009 (1.003–1.016)*	1.004 (0.999–1.009)	SO ₂ , CO, NO ₂ , PM10, Temp_avg
	PM10 (µg/m ³)	1.004 (1.000–1.007)	1.007 (1.003–1.011)*	1.005 (1.002–1.008)*	SO ₂ , CO, O ₃ , PM10, Temp_avg
	Temperature avg. (10 °C)	1.000 (0.999–1.001)	0.998 (0.997–1.000)	0.999 (0.998–1.000)	SO ₂ , CO, O ₃ , NO ₂ , Temp_avg
	Daily range (10 °C)	0.996 (0.987–1.004)	0.997 (0.988–1.006)	0.998 (0.990–1.006)	CO, O ₃ , NO ₂ , PM10, humidity, Atmos_press
	Relative humidity (%)	1.004 (0.995–1.014)	1.008 (0.999–1.018)	1.009 (1.000–1.019)	
	Air pressure (hPa)	1.000 (0.979–1.020)	0.996 (0.976–1.017)	0.986 (0.966–1.007)	Temp_avg, Atmos_press
		1.001 (0.949–1.057)	0.994 (0.942–1.048)	1.011 (0.958–1.068)	Temp_avg, humidity
				0.986 (0.933–1.042)	

*p values <0.05.

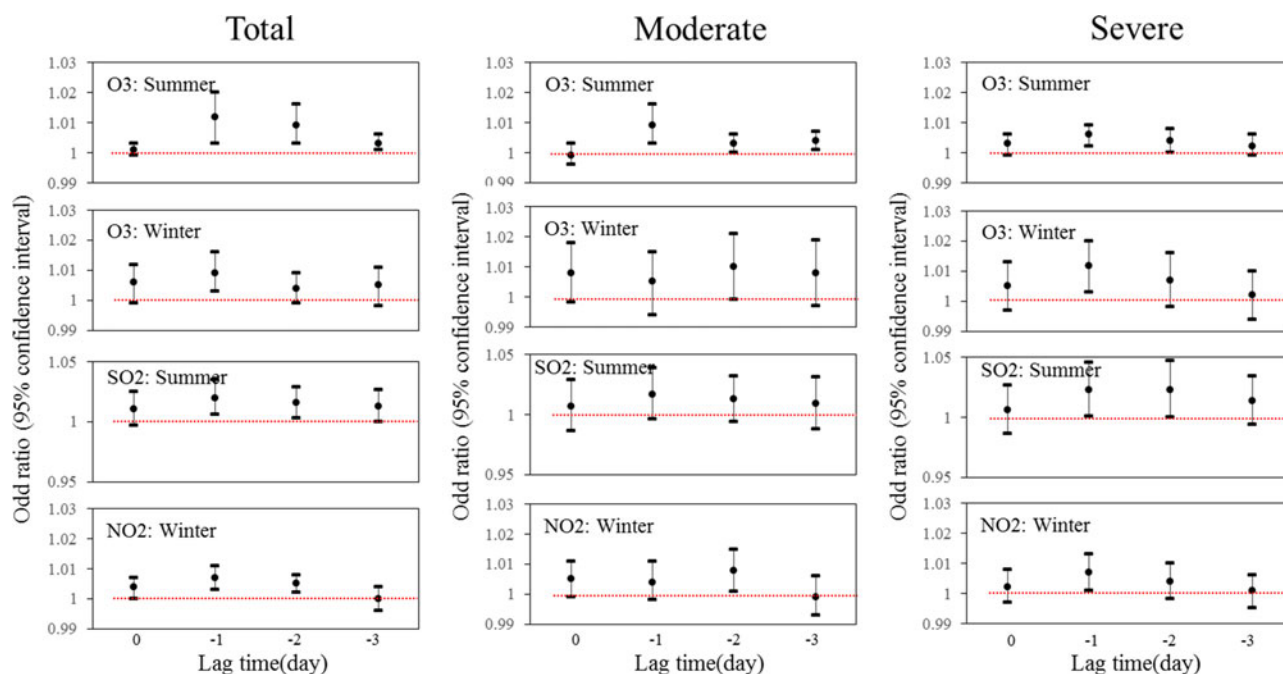


Figure 1. Effect of air pollution and meteorological condition on exacerbation.

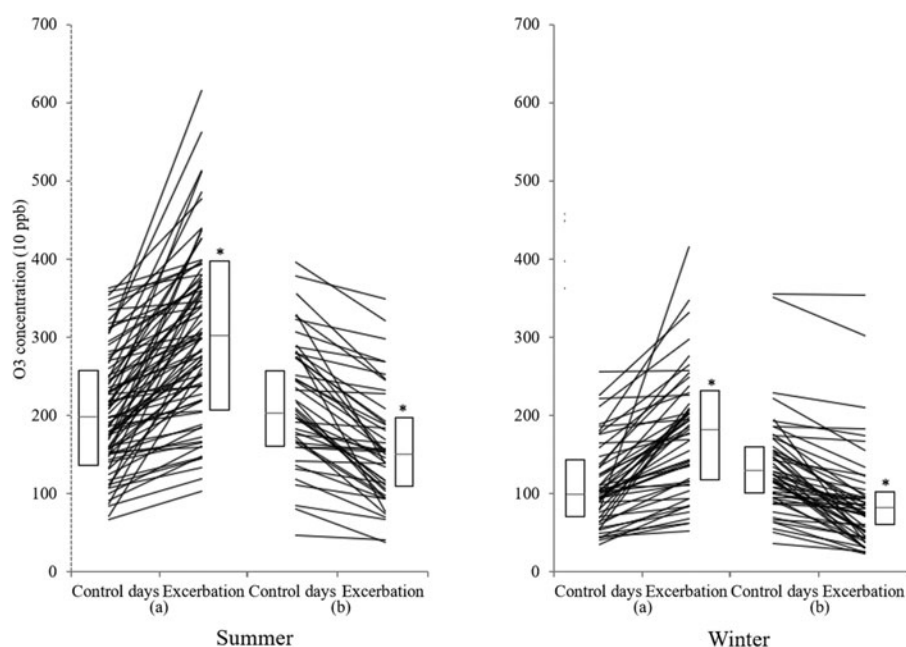


Figure 2. Comparisons of O_3 levels on exacerbation days with those on control days in summer and winter. Solid lines indicate cases in which O_3 levels were higher than those of control day and dashed lines indicate vice versa. Box plots indicate medians and interquartile ranges of O_3 levels. In the summer, 63.2% of episodes (81 out of 128) occurred when the O_3 concentration on T1 was significantly higher than that on control days, while only 51% of exacerbation episodes (54 out of 107) occurred in winter. * $p < 0.0001$, # $p < 0.0001$.

well, there was a positive association between the exacerbation episodes among all study subjects and increased O_3 levels during the winter, summer, and spring (Table S5).

Discussion

The present study showed that O_3 and NO_2 concentrations during the winter and O_3 and SO_2 concentration during the summer were significantly associated

with asthma exacerbations in adult patients. This result supports the relationship of air pollutants and meteorological conditions with exacerbations in adult asthmatics: O₃, NO₂, CO and PM_{2.5} are significantly associated with hospital admissions and EDVs in a recent meta-analysis (11) and epidemiologic studies of Korean asthmatic children under 15 years of age (34,35). Of these factors, O₃ showed the most significant association with exacerbations in both the winter and summer. In addition, only O₃ levels all through years were associated with the total exacerbations in the present study (Data not shown).

Deleterious effects of O₃ exposure on health, and particularly the lungs, are evident in both human studies and animal experiments (36–39). Exposure to high levels of O₃ increases EDV and hospital admission rates among asthmatics (40) and COPD patients (41–43). In the present study, the effect of O₃ on the number of asthma exacerbations was apparent in both winter and summer: the relative risks were 1.2% and about 1%/10 ppb increase in O₃, respectively. This rate shows slightly lower trend when compared with the previously reported rate in 90,381 Korean childhood asthmatics for hospitalizations (4.6%/10 ppb increase of O₃) (34), and that of 92,535 EDV for overall asthmatics in Korea during the summer of 2002 (2.85% per 10 ppb increase of O₃) (35,44). The rate of EDVs for asthma exacerbations varies depending on age: about five times higher in children under 9 years of age compared with adults aged between 40 and 70 years in Korea (5.45% vs. 0.009–1.16%) (35). It is well known that children are more vulnerable than adult to the adverse effects of air pollution. Since their lungs and immune systems are not fully developed, children breathe more air per unit body weight; furthermore, their peripheral airways are anatomically smaller than adult so that inflammation results in relatively greater airway obstruction (45–47). In addition, children have higher levels of exposure to air pollutants than adults mainly because they spend more time outdoors and have a higher level of physical activity (48).

Interestingly, the effect of O₃ on asthma exacerbations seems to be greater during the summer than winter. Determining a direct relationship between O₃ exposure and asthma exacerbation episodes requires analysis of the temporal relationship between O₃ concentrations and the time of onset of exacerbations. In the present study, the frequency of temporal relation was marginally higher in the summer than the winter although statistically insignificant ($p = 0.064$). In addition, O₃ levels were significantly higher in summer

than winter. These data suggest that the relationship between asthma exacerbations and O₃ levels may be stronger during the summer compared with that during the winter. This result is in a good agreement with studies of childhood asthmatics. In a study on children aged from 5 to 17 years (91,386 EDVs), drawn from 41 hospitals in metropolitan Atlanta, USA during 1993–2004, ozone was strongly associated with EDVs during the summer (49). In other studies, decreases in lung function, use of a rescue inhaler and the number of EDVs among pediatric asthmatics were also associated with increases in O₃ in summer (50,51).

In addition, the association of O₃ levels with asthma exacerbations in winter may be affected by other risk factors for asthma exacerbations, especially respiratory viral infections in winter season. The effects of O₃ are significantly greater in individuals with a preexisting respiratory viral infection because of a synergism between O₃ levels and rhinovirus infection in terms of cytokine production by human bronchial epithelial cells (52). Thus, the association of O₃ levels on exacerbation episodes during the winter season in the present study might be attributed to the co-occurrence of respiratory viral infections, which should be studied in the near future.

Besides O₃, levels of NO₂ during the winter and SO₂ in the summer were strongly associated with exacerbations. Associations of NO₂ and SO₂ with exacerbations were seen in the previous meta-analysis of exacerbations (11). In addition, early life exposure to NO₂ and SO₂ was associated with childhood asthma (10). We also previously observed that SO₂ levels and low temperatures during the winter were associated with exacerbations among adult refractory asthmatics (18). Ozone is a secondary pollutant formed by photochemical reactions between sunlight and pollutant precursors such as nitrogen oxides and volatile organic compounds (53). Thus, as a precursor to O₃, NO₂ may trigger bronchial inflammation (54) and the effect of O₃ on exacerbation may be dependent on NO₂ levels and temperature. Nitrogen oxides, including nitrogen dioxide, are formed primarily by the reaction of ozone with nitric oxide emitted during fossil fuel combustion. The main sources of sulfur oxides are primary emissions during energy production or industrial processes. In Korea, a huge amount of fossil fuel combustion has occurred during winter season due to cold temperature. However, the levels of NO₂ were similar through the four seasons and that of SO₂ was low in summer compared to those of the other seasons. Thus, we analyzed correlations

between the pollutants and the meteorological factors. However, O_3 levels were negatively correlated with NO_2 levels in the summer of the present study ($r = -0.185$, $p = 0.039$), but were not correlated with temperature ($r = 0.009$, $p = 0.917$). Furthermore, a negative correlation between O_3 and NO_2 levels has been observed in other studies (55,56). In addition, O_3 levels were negatively correlated with SO_2 , CO, PM10 and temperature in the present study (Table S3). These data indicate that NO_2 , SO_2 , and temperature may not act as a proxy for other pollutants, instead independently contributing to exacerbations.

Although air pollutants have typically been considered as a cause of exacerbations, their impact is generally recognized to be much less than that of viruses and allergen sensitization (57). Even among adults, 50–60% of asthma exacerbations are associated with upper respiratory viral infections (58) and rhinovirus is the most common cause of exacerbations during the winter, and where the present study was conducted during this season (59). O_3 and NO_2 increase the susceptibility of asthmatics to respiratory viral infections (58). Allergens are one of the most important triggers of asthma exacerbations (57). Due to being sensitized to house dust mites and fungal allergens, asthmatics show a greater airway response upon exposure to air pollutants (60,61). In the present study, the proportion of subjects sensitized to allergens, including house dust mites, pollens, and fungi, was not different among the four seasons, nor according to the severity of asthma (Table S6). This indicates that air pollutant-associated exacerbations may not be associated with allergen sensitization.

In our previous study of patients with RA, a decrease in temperature and increase in SO_2 level during the winter increased the risk of RA exacerbation (18). This result is not in agreement with that of the present study. The previous study included 238 exacerbation episodes, occurring between 2005 and 2009, of 39 nonsmoking RA patients experiencing multiple episodes of exacerbations that required an increase in asthma medications including systemic steroids. In contrast, the present study included 618 exacerbation episodes, occurring between 2005 and 2015, of 143 nonsmoking asthmatics. There was no difference in the mean age, BMI, or gender distribution between the two studies. However, the mean initial FEV1 in the previous study was significantly lower than that in the present study (55% vs. 68%), despite treatment with higher doses of inhaled steroids. These data suggest that the effect of air pollutants and

meteorological conditions may differ according to airway obstruction status in asthmatics.

There are several limitations in the present study. Interestingly, there was no difference in the levels of these pollutants between severe exacerbation and moderate exacerbation episodes. Absence of difference might be due to the following limitation factors. First, we obtained only outdoor measurements of air pollutants for the evaluation of individual exposure levels. Since individuals spend most of their time indoors, a change in the indoor environment may be a significant contributor to an increased risk of asthma exacerbations. Indoor and/or occupational pollutant exposure levels and the duration of exposure around the time of each exacerbation episode should be considered as demonstrated in a previous study (62).

In our study, the exposure modeling method of which meteorological data and air pollution data were obtained from the national monitoring site closest to the address of each patient was used. The median distance with interquartile ranges of 143 pollutant monitoring sites was 1.457 km (with interquartile of 0.916 and 2.141 km) and that of 143 weather monitoring sites was 12.551 km (with interquartile of 10.164 and 14.666 km). Thus other exposure modeling methods like inverse distance weighted method (IDW) (63,64) and land-use regress method (LUR) will be applied as the next analysis (10,65). Secondly, the degree of pollen exposure was not assessed in the present study. Further investigation of these variables will further clarify the factors involved in asthma exacerbations. Thirdly, the study used a retrospective design and included a relatively small sample size compared with most previous epidemiologic studies that used medical records of several hospitals or National Health Insurance (KNHI) data having sample sizes of up to 10,000. However, these studies did not obtain detailed information on temporal relationship; in contrast, we had access to relationship between the two variables. Fourthly, we did not observe the effect of PM2.5 because it has been measured after 2015 in Korea.

Conclusion

We examined the effect of air pollution on the occurrence and severity of asthma exacerbations among currently nonsmoking adult asthmatics and confirmed significant associations of O_3 , SO_2 and NO_2 levels with asthma exacerbation. However, the severities of the exacerbation may not be related with the levels of these pollutants.

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Declaration of interest

There are no financial or other issues that might lead to conflict of interest.

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