

ENVIRONMENTAL DETERMINANTS

Winter Season Temperature Drops and Sulfur Dioxide Levels Affect on Exacerbation of Refractory Asthma in South Korea: A Time-Trend Controlled Case-Crossover Study Using Soonchunhyang Asthma Cohort Data

SUNGROUL KIM, PH.D.,^{1,*} YONGBAE KIM, M.D., PH.D.,² MEE-RI LEE, M.D.,² JUNHYOUNG KIM, B.A.,¹ ARA JUNG, B.A.,¹ JONG SOOK PARK, M.D.,³ AN-SOO JANG, M.D., PH.D.,³ SUNG-WOO PARK, M.D.,³ SOO-TAEK UH, M.D.,⁴ JAE SUNG CHOI, M.D.,⁵ YOUNG HOON KIM, M.D.,⁵ TIMOTHY BUCKLEY, PH.D.,⁶ AND CHOON-SIK PARK, M.D.³

¹Department of Environmental Health Sciences, Soonchunhyang University, Asan, South Korea.

²Department of Preventive Medicine, Soonchunhyang University, Asan, South Korea.

³Division of Allergy and Respiratory Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea.

⁴Division of Respiratory and Allergy Medicine, Soonchunhyang University Seoul Hospital, Seoul, South Korea.

⁵Division of Allergy and Respiratory Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, South Korea.

⁶College of Public Health, Ohio State University, Columbus, OH, USA.

Objective. According to the American Thoracic Society, approximately 5% of all asthmatics have refractory asthma (RA); these patients fail to recover lost lung function even after long-term treatment with high doses of medications. **Methods.** Using a time-trend controlled case-crossover study design, we calculated odds ratios to evaluate whether exposure to ambient air pollutants and certain meteorological conditions on the day of admission (Lag 0) and up to 3 days before admission (Lag 1 through Lag 3) were associated with acute RA exacerbation. Results were obtained after controlling for the effects of seasonality, smoking, and allergen sensitivity; we stratified our data into four seasons with respect to the median temperature of each month and further stratified them according to self-reported smoking status and skin-prick test results. **Results.** In our study, RA patients ($n = 82$), living in metropolitan city of Seoul and Kyunggi Province, accounted for 3.7% of all asthmatics ($n = 2298$) registered in our asthma cohort between 2005 and 2009. In winter, a 1°C decrease in ambient temperature and a 1 ppb increase in sulfur dioxide concentration on the day of Lag 1 were associated with 14.8% (95% confidence interval [CI]: 0.9–26.7) and 19.7% (95% CI: 3.3–38.7) increases in the risk of RA exacerbation among nonsmokers, respectively. Similar associations were obtained on the day of Lag 2. The association remained unchanged after excluding patients sensitive to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. **Conclusions.** Exposure to temperature drops and increased sulfur dioxide concentrations are positively associated with the occurrence of acute RA exacerbation during winter with 1 or 2 day lags.

Keywords asthma exacerbation, case-crossover study, refractory asthma, sulfur dioxide, temperature

INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by airflow limitation and airway hyperresponsiveness (1). This disease can be separated into several subgroups according to the etiology, pathology, severity, and responsiveness to treatment (2). Prolonged treatment with a high dose of inhaled corticosteroids can relieve airflow obstruction in asthmatics. However, the American Thoracic Society (ATS) states that even after long-term treatment with high doses of corticosteroids and additional medications, some patients fail to completely recover lost lung function such that airflow is persistently obstructed; this is known as refractory asthma (RA). This specific phenotype of asthma makes up approximately 5% of total asthma cases (3). This subgroup is characteristically difficult to treat and requires high levels of medication to control persistent

symptoms; exacerbations and airflow obstructions persist despite the use of high or maximal doses of medication. Acute exacerbations of RA can lead to such severe airway obstruction that mechanical ventilation is required as a life-saving measure. Thus, knowing the risk factors for RA is important for minimizing both the need for emergency medical interventions and disruption of daily activities (4).

Many studies demonstrate associations between hospital admissions for respiratory conditions and acute exposure to air pollution (5–9). Ozone is associated with increased asthma-related hospital admissions and emergency department visits among children and adults (10, 11). Several studies also suggest that exposure to NO_x or SO₂ is associated with an increased risk of respiratory illness, including asthma, among children (12–14). Similarly, acute exposure to airborne particles is associated with emergency department visits for mild asthma (15, 16). Several different environmental and behavioral factors, including viral infection, allergen sensitization, weather conditions, exercise, smoking, and diet, have been potentially associated with the asthma morbidity (17–22).

*Corresponding author: Sungroul Kim, Ph.D., Department of Environmental Health Sciences, Soonchunhyang University, 646 Shinchang-myeon, Asan, 336-745 South Korea; Tel: +82415301249; Fax: +82415301272; E-mail: srkimehs@jsch.ac.kr

Moreover, studies in South Korea indicate that increases in the incidence of mortality from respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD) are related to acute exposure to high levels of air pollutants, including ozone and/or PM₁₀ (23–26).

The association between acute exposure to environmental factors and the development of asthma is clearer than such associations with RA. Studies examining the associations between RA exacerbation, ambient air pollution, and meteorological conditions are limited (27, 28). Specific epidemiologic studies have been requested by the ATS (3) to assess the prevalence of RA and evaluate the distribution of RA subtypes among asthma patients. Such a study was conducted in Europe (29), but few similar studies have been conducted in Asia where seasonal, environmental, and ethnic factors are likely to differ from those in Europe. In addition, it was recently reported that climate variability, including a high frequency of hotter summers and colder winter days, is increasing—likely as a result of climate change, fossil fuel combustion, and greenhouse gas emissions (30). Such climate variability may affect the concentrations and distributions of air pollutants, which may interfere with the normal seasonal cycle of meteorological conditions (30). In this study, we assessed the prevalence of RA and evaluated the association between acute exposure to ambient air pollution and meteorological conditions with acute exacerbation of RA after controlling for smoking and seasonality.

METHODS

Study Population

We retrospectively studied the clinical data of 2298 adults with asthma, aged 19–87 years, who had been registered since 2005. All subjects were followed for a minimum of 2 years in an asthma cohort from the Genome Research Center for Allergy and Respiratory Diseases, Soonchunhyang University Bucheon Hospital, South Korea. The study subjects were recruited from three tertiary hospitals: Soonchunhyang University Bucheon Hospital, Seoul Hospital, and Cheonan Hospital. The diagnosis of asthma was based on the Global Initiative for Asthma (GINA) guidelines (1). All subjects had a clinical diagnosis of asthma supported by one or more of the following criteria: (i) an increase in forced expiratory volume in 1 s (FEV₁) > 15% after inhalation of 200 µg albuterol; (ii) a 20% reduction in FEV₁ in response to a provocative concentration of <10 mg/mL inhaled methacholine (PC20); or (iii) an increase in FEV₁ > 20% over 14 days with inhaled corticosteroid use. All subjects underwent a standardized examination including analysis of sputum specimens, blood (with differential counts), IgE levels, chest posterior–anterior radiography, allergy skin-prick tests, and spirometry. Twenty-four common inhalant allergens, including dust mites (*Dermatophagoides farinae* [DF] and *Dermatophagoides pteronyssinus* [DP]), cat fur, dog fur, cockroaches, grass pollens, tree pollens, ragweed pollens, and *Aspergillus* species (Bencard Co.,

Brentford, UK), were used in skin-prick tests. Additional information including demographics and body mass index (BMI) was also recorded.

According to the criteria defined by the ATS (3) and GINA (1), in our cohort, we classified a patient as a RA patient if the patient's clinical outcomes met one or both major criteria (i) treatment with continuous or near-continuous (50% of 1 year) oral corticosteroids and (ii) requiring treatment with high-dose inhaled corticosteroids (>880 µg fluticasone propionate per day), and any two of the following minor criteria: (i) requiring daily treatment with a controller medication in addition to inhaled corticosteroids, (ii) asthma symptoms requiring short-acting β-agonist use on a daily or near-daily basis, (iii) persistent airway obstruction (FEV₁ ≤ 80%), (iv) one or more urgent care visits for asthma per year, (v) three or more oral steroid “bursts” per year, (vi) prompt deterioration with ≤25% reduction in oral or inhaled corticosteroid dose, and (vii) near-fatal asthma event in the past. According to the criteria defined by the ATS (3) and GINA (1), among the subjects who had attended regular follow-ups over a 2 year or longer period since 2005, 98 patients were diagnosed with RA.

In our study, we included only the 82 patients living in the metropolitan city of Seoul or Kyunggi Province, South Korea, who presented at the Soonchunhyang Hospital between 2005 and 2009 with multiple episodes of exacerbations, requiring an increase in asthma medications including systemic steroids. Our final data comprised 238 episodes from 39 RA nonsmoking patients and 283 episodes from 43 RA smoking patients. In brief, in our study, exacerbation of asthma was defined as an episode of progressive increase in shortness of breath, wheezing, or chest tightness and decrease in expiratory airflow; clinically, it was defined as post-bronchodilator PEF or FEV₁ of <80% of the predicted value or personal best. The RA patients' average (±standard deviation) initial FEV₁ (% predicted) was 55 (±8), and their average (±standard deviation) daily dose of inhaled steroids (fluticasone propionate equivalent) was approximately 1300 µg (±120) per day. Demographic information was collected from registration documents submitted by the patients on the first day of their hospital visits since 2005.

We excluded patients who had COPD, vocal cord dysfunction, obstructive sleep apnea, Churg–Strauss syndrome, cardiac dysfunction, and allergic bronchopulmonary aspergillosis (ABPA) as well as those who adhered poorly to treatment procedures. Study procedures related to human subjects and informed consent were approved by the research ethics committee of the Soonchunhyang University Bucheon Hospital.

Meteorological and Air Pollution Data

Meteorological data including mean daily temperatures, relative humidity, and air pressure were obtained at the national monitoring sites closest to the hospital (24). Air pollution measurements were obtained from the national ambient monitoring station located closest to each patient's home address. Daily (24 h) averages for particulate matter with an aerodynamic diameter <10 µm (PM₁₀),

sulfur dioxide (SO₂), and nitrogen dioxide (NO₂) were used, whereas 8 h running averages were used for ozone (O₃) and carbon monoxide (CO).

Statistical Analysis

To evaluate the impacts of exposure to ambient air pollution and meteorological conditions on RA exacerbation, we used a time-trend controlled symmetrical, bidirectional, case-crossover design with conditional logistic regression models. Each episode corresponds to a diagnosis of exacerbation with shortness of breath, wheezing, or chest tightness and decrease in expiratory airflow; clinically, it was defined as post-bronchodilator PEF or FEV₁ of <80% of the predicted value or personal best and usage of high doses of inhaled steroids. We constrained an “episode” to have a frequency no greater than one visit per month to avoid attributing follow-up visits to new independent episodes (31). Symmetrical and bidirectional control selection was conducted to control time trends (32); 4 control days were selected at fixed intervals of 7 and 14 days before and after the day of each episode such that all control days fell on the same day of the week.

The distributions of meteorological conditions and air pollution concentrations on the day of admission of each episode were compared with those of selected controls (± 7 and 14 days per episode day), using the Wilcoxon rank-sum test. The effects of meteorological factors and air pollution levels on exacerbation were evaluated on the day of admission (Lag0) and up to 3 days before admission (Lag1 through Lag3), using a conditional logistic regression model. Odds ratios (ORs) for exposure were calculated to estimate the increased risk of RA exacerbation according to unit increases in air pollution and meteorological condition levels (31, 33).

Three different models were run. The first model included air pollution and meteorological factors and included all patients—both smokers and nonsmokers—after controlling for seasonality. We stratified the data into four seasons: spring (March–May), summer (June–August), fall (September–November), and winter (December to February) with respect to the monthly median temperature. The second model included the same environmental risk factors stated above but analyzed the smoking and nonsmoking RA patient groups separately after stratifying the data by season and self-reported smoking status. The final model was conducted after stratifying the data by season, self-reported smoking status, and the most commonly detected allergens in the skin-prick test among patients.

Because we were only interested in the impact of exposure to air pollution and meteorological conditions, we mainly presented the significant results obtained from data of the nonsmoking RA patient group. However, the results of all three models for both smoking and nonsmoking patients by season are presented in the Supplemental Materials (Supplementary Tables 1 to 6 available online at <http://informahealthcare.com/doi/suppl/10.3109/02770903.2012.702839>).

Multiple sensitivity analyses were conducted. First, we ran several single-pollutant models focusing on the impact of exposure to single air pollutants after adjusting for the effect of exposure to meteorological conditions in all episodes of exacerbations experienced by nonsmoking RA patients. Second, we examined the implications using data obtained from all patients (both nonsmokers and smokers). All analyses were conducted using the SAS 9.1 package.

RESULTS

Between 2005 and 2009, a total of 238 and 283 episodes from 39 and 43 self-identified nonsmokers and smokers were recorded, respectively (Table 1). Among nonsmoking patients who experienced RA episodes, females were predominant in all seasons, making up 71.8–85.4% of the population. Meanwhile, males were predominant among smokers, making up 65–76% of the population by season. The medians (interquartile ranges [IQRs]) of patients' ages ranged from 53 to 58 years for nonsmokers and 58 to 62 years for smokers. The BMI over the seasons ranged from 22.0 to 23.1 kg/m² and 24.0 to 25.2 kg/m² for nonsmokers and smokers, respectively (Table 1).

Skin-prick tests revealed that higher proportions of both nonsmoking and smoking patients exhibited sensitivity to DF or DP, compared with other allergens. Among nonsmokers, the percentage of episodes having sensitivity to DF and DP ranged from 17% to 24% and 14% to 20%, respectively while, among smokers, the percentages ranged from 4% to 7% and 11% to 17%, respectively.

Table 2 summarizes descriptive statistics showing that the levels of most environmental factors at the time of admission for the episodes (Lag0) among nonsmoking RA patients were not significantly different from those of control days. However, the mean PM₁₀ concentration at the time of episodes was 73.0 $\mu\text{g}/\text{m}^3$, which differed significantly from that of control days (66.5 $\mu\text{g}/\text{m}^3$; $p = .021$ for spring). Among smokers, the levels of all environmental factors during episodes were not significantly different from those of control days (data not shown).

The data stratified by season and smoking status showed that in multi-pollutant models with smoking RA patients, there was no significant association between the exacerbation of RA and changes in air pollutant levels or meteorological conditions in any season except for relative humidity on Lag0 in spring and Lag3 in summer (Supplementary Table 1). Similarly, for nonsmoking RA patients, no association was observed in spring, summer, or fall except for CO on day Lag1 in spring and air pressure on Lag1 in fall (Supplementary Table 2).

However, in multi-pollutant models among nonsmokers, in winter, a 1°C decrease in ambient temperature and a 1 ppb increase in SO₂ concentration significantly increased RA exacerbation on Lag1 and Lag2 after controlling for other explanatory variables: 14.8% (95% confidence interval [CI]: 0.9–26.7) for temperature and 19.7% (95% CI: 3.3–38.7) for SO₂, and 28% (95% CI: 13.7–39.9)

TABLE 1.—Descriptive summary of the distribution of episodes, demographic information, and number of episodes in allergen skinsensitizations by season.

	All		Spring		Summer		Fall		Winter	
	NS	S	NS	S	NS	S	NS	S	NS	S
Total number of episodes [patients], 2005–2009	238 [39]	283 [43]	64 [30]	65 [30]	62 [22]	72 [32]	71 [28]	71 [34]	41 [24]	75 [29]
Age										
Median (IQR)	54 (44–64)	60 (52–65)	55 (45–64)	62 (54–68)	54 (43–64)	58 (47–63)	53 (42–64)	58 (49–66)	58 (50–65)	60 (54–63)
>65 years (%)	20.2	24.0	20.3	35.4	19.3	16.7	19.7	25.3	21.9	21.3
Sex										
Female (%)	79.3	27.9	84.0	35.4	85.4	25.0	71.8	28.2	78.5	24.0
BMI (kg/m ²)										
Median (IQR)	22.0 (21.2–24.6)	24.6 (21.8–26.8)	23.1 (21.6–25.5)	24.5 (22.2–26.3)	22.0 (20.7–24.3)	24.0 (21.6–27.1)	22.9 (21.1–24.6)	25.2 (21.3–27.4)	22.5 (21.3–24.3)	24.8 (21.9–26.7)
>25 (%)	19.6	43.8	28.1	44.6	22.9	37.5	19.7	50.7	17.1	45.3
Number of episodes [patients] (% positive in allergen skin-prick test)										
DF	49 [7] (21)	16 [5] (6)	13 [7] (20)	3 [2] (5)	15 [4] (24)	5 [4] (7)	12 [5] (17)	3 [2] (4)	9 [5] (22)	5 [3] (7)
DP	40 [7] (17)	40 [9] (14)	12 [7] (19)	9 [4] (14)	9 [4] (15)	12 [5] (17)	11 [5] (14)	11 [6] (15)	8 [5] (20)	8 [5] (11)
DF or DP	57 [8] (24)	40 [9] (14)	16 [8] (25)	9 [4] (14)	16 [5] (26)	12 [6] (17)	14 [6] (20)	11 [6] (15)	11 [6] (27)	8 [5] (11)
Mixed mold	–	2 [1] (1)	–	–	–	–	–	2 [1] (3)	–	–
Chrysanthemum	5 [2] (2)	2 [1] (1)	2 [2] (3)	–	–	–	2 [1] (3)	2 [1] (3)	1 [1] (2)	–
Grass pollens	–	–	–	–	–	–	–	–	–	–
Mixed tree pollen	25 [4] (11)	3 [2] (1)	7 [4] (11)	–	8 [2] (13)	–	6 [3] (8)	3 [2] (4)	4 [2] (10)	–
Dog hair	4 [2] (25)	2 [1] (1)	2 [1] (3)	–	1 [1] (2)	–	1 [1] (1)	2 [1] (3)	–	–
Cat fur	26 [3] (2)	–	8 [3] (13)	–	8 [2] (13)	–	5 [2] (7)	–	5 [2] (12)	–
Cockroach	1 [1] (1)	–	1 [1] (2)	–	–	–	–	–	–	–

Note: NS, nonsmokers; S, smokers; DF, *Dermatophagoides farinae*; DP, *Dermatophagoides pteronyssinus*.

Mixed mold: *Alternaria alternata*, *Aspergillus fumigatus*, *Aspergillus niger*; Mixed tree pollen: Plain pollen, willow pollen, poplar pollen, locust, lilac pollen, hazel pollen, alder pollen, elder pollen, birch pollen, beech pollen, ragweed pollen, mugwort pollen.

TABLE 2.—Descriptive summary of baseline meteorological factors and air pollutants by season in nonsmoking patients.

Conditions on specified day	Spring	Summer	Fall	Winter
Day of admittance with the episode				
<i>Meteorological factor</i>				
Temperature (°C)	11.5 (8.0–15.2)	23.1 (22.2–25.1)	16.0 (9.3–20.8)	1.4 (–0.4–3.3)
Relative humidity (%)	62.9 (53.6–72.6)	76.8 (66.9–86.6)	67.7 (59.6–75.3)	59.5 (54.0–70.9)
Air pressure (hPa)	1014.5 (1011.3–1018.2)	1007.1 (1003.7–1010.9)	1016.8 (1013.6–1022.5)	1023.6 (1019.7–1026.3)
<i>Air pollutant</i>				
SO ₂ (ppb)	7.1 (4.5–9.1)	5.1 (4.0–6.6)	5.8 (4.4–8.3)	9.3 (6.5–12.2)
PM ₁₀ (µg/m ³)	73.0 (51.2–88.8) ^a	48.1 (29.8–69.0)	48.7 (35.0–65.5)	62.9 (52.8–96.3)
Ozone (ppb)	28.0 (18.8–38.6)	25.7 (16.4–33.1)	18.2 (12.0–23.5)	9.1 (6.7–18.5)
CO (0.1 ppm)	5.8 (4.8–7.0)	4.4 (3.3–5.9)	5.1 (3.7–7.3)	8.5 (5.9–11.4)
NO ₂ (ppb)	34.3 (26.1–41.3)	26.6 (19.9–35.3)	30.6 (22.6–42.0)	38.8 (31.3–46.8)
Control days (7 and 14 days before and after each episode)				
<i>Meteorological factor</i>				
Temperature (°C)	11.5 (6.7–16.1)	23.2 (21.2–25.1)	15.6 (10.2–20.4)	1.6 (–2.1–4.2)
Relative humidity (%)	61.0 (51.2–71.2)	78.0 (68.3–85.5)	67.9 (61.8–77.4)	59.1 (50.5–71.3)
Air pressure (hPa)	1014.6 (1010.6–1019.4)	1007.8 (1003.6–1010.8)	1017.3 (1013.5–1020.8)	1024.9 (1021.8–1027.9)
<i>Air pollutant</i>				
SO ₂ (ppb)	6.9 (4.9–9.0)	4.9 (3.7–6.3)	6.5 (4.2–8.5)	8.8 (6.5–11.5)
PM ₁₀ (µg/m ³)	66.5 (51.0–91.9)	47.8 (31.3–68.9)	52.6 (38.0–74.8)	60.8 (45.0–87.1)
Ozone (ppb)	28.3 (20.3–35.8)	24.3 (16.8–32.3)	16.7 (12.0–22.3)	10.9 (6.5–16.5)
CO (0.1 ppm)	5.6 (4.5–7.0)	4.4 (3.4–5.7)	5.2 (4.0–7.2)	8.3 (6.1–11.4)
NO ₂ (ppb)	32.7 (24.5–41.4)	26.0 (18.9–35.2)	30.6 (22.8–41.6)	37.7 (26.1–48.9)

Note: Results are reported as median (IQR)

^aSignificantly different from the relevant term ($p = .021$ for spring).

for temperature and 16.4% (95% CI: 3.0–31.6) for SO₂, respectively (Table 3). Furthermore, even after excluding the episodes in patients sensitive to DF or DP, by stratifying nonsmoking patient data, model results revealed a statistically significant impact of temperature and SO₂ on RA exacerbation on Lag2: 33.1% (95% CI: 14.3–46.2) for temperature and 16.2% (95% CI: 3.0–32.3) for SO₂ (Table 3). This association did not change in the multi-pollutant model for all episodes (i.e., both smokers and nonsmokers); however, we did not observe any significant impact of temperature and SO₂ on RA exacerbation among smokers in winter (Figure 1).

Furthermore, in winter, the single-pollutant model results also showed a positive association between RA exacerbation among nonsmoking patients exposed to increased SO₂ or decreased temperature on the days Lag1 and Lag2 (Supplementary Table 6), confirming our multi-pollutant modeling outcomes. A 1°C decrease in ambient temperature was associated with a 16.1% (95% CI: 4.1–26.6) increase in the risk of RA exacerbation after controlling for the effects of humidity, air pressure, and SO₂. In addition, a 14.7% (95% CI: 1.9–29.2) increase in the incidence of RA exacerbation was associated with a 1 ppb increase in SO₂ concentrations on the day of Lag1.

DISCUSSION

In this study, we observed that exposure to a wintertime temperature drops or increased SO₂ concentrations was associated with an increased incidence of RA exacerbation with 1–2 day lags in nonsmoking adult patients. When we analyzed our data without controlling for seasonality, no

single variable was associated with the risk of RA exacerbation on episode days compared with control days (data not shown).

Nakaji *et al.* (34) report that seasonality significantly interacts with RA exacerbation. They report that in Japan, seasonal changes strongly influence the incidence of respiratory diseases, including pneumonia and influenza, as well as other diseases such as heart and cerebrovascular diseases; the highest incidences of these diseases occur during winter (34). Our results indicate a seasonal effect similar to that reported by Nakaji *et al.*; in winter, RA exacerbation was significantly associated with exposure to temperature drops with lag effects, while no associations were found in other seasons. Our results are also concordant with the recent results of May *et al.*, who report that the need for admission due to asthma is associated with exposure to decreasing temperature (25).

Our study results were also corroborated by those of other observational studies reporting that cooling enhances airway inflammation, resulting in airway narrowing and asthma exacerbation (35). Abe *et al.* (36) found that lower minimum ambient temperature is a significant risk factor associated with asthma exacerbation in adults. McDonald *et al.* (37) also report that cooling of the skin is associated with asthma exacerbation. Regarding the impact of climate change on health, especially respiratory diseases, unexpected winter temperature drops should be monitored carefully to minimize their impact on human respiratory health in East Asia.

Furthermore, the present results show smaller or non-significant effects of SO₂ and cold temperature exposure on smoking RA patients compared with nonsmoking RA patients. This implies that smoking modifies the acute

TABLE 3.—Impact of exposure to air pollution and meteorological conditions on exacerbation of RA in nonsmoking patients in winter.

	Adjusted OR (95% CI) using conditional logistic regression models							
	Multi-pollutant model 1 ^a				Multi-pollutant model 2 ^b			
	Lag 0	Lag 1	Lag 2	Lag 3	Lag 0	Lag 1	Lag 2	Lag 3
Temperature (°C)	1.042 (0.894–1.215)	0.852 (0.733–0.991)	0.720 (0.601–0.863)	0.860 (0.754–0.982)	1.056 (0.886–1.259)	0.870 (0.725–1.045)	0.679 (0.538–0.857)	0.884 (0.762–1.026)
Relative humidity (%)	0.973 (0.935–1.012)	1.036 (0.996–1.073)	1.012 (0.995–1.057)	1.014 (0.974–1.055)	0.979 (0.934–1.026)	1.032 (0.988–1.079)	1.137 (1.055–1.224)	0.994 (0.951–1.039)
Air pressure (hPa)	0.962 (0.878–1.053)	0.983 (0.882–1.096)	0.993 (0.888–1.110)	0.948 (0.872–1.031)	0.957 (0.860–1.064)	1.031 (0.899–1.181)	0.966 (0.839–1.111)	0.935 (0.849–1.029)
SO ₂ (ppb)	1.160 (0.999–1.344)	1.197 (1.033–1.387)	1.164 (1.030–1.316)	1.019 (0.897–1.158)	1.198 (1.012–1.418)	1.216 (1.002–1.475)	1.162 (1.020–1.323)	1.043 (0.903–1.204)
PM ₁₀ (µg/m ³)	1.007 (0.991–1.023)	0.989 (0.970–1.008)	0.996 (0.982–1.009)	0.997 (0.985–1.008)	1.003 (0.983–1.023)	0.987 (0.964–1.01)	0.990 (0.974–1.006)	0.998 (0.989–1.007)
O ₃ (ppb)	0.914 (0.826–1.012)	0.930 (0.829–1.044)	1.068 (0.953–1.197)	0.972 (0.877–1.077)	0.838 (0.720–0.975)	0.826 (0.701–0.973)	1.050 (0.913–1.206)	0.936 (0.823–1.064)
CO (0.1 ppm)	0.965 (0.869–1.073)	0.944 (0.813–1.096)	0.953 (0.809–1.123)	1.004 (0.960–1.051)	0.959 (0.837–1.099)	0.959 (0.837–1.098)	0.968 (0.847–1.105)	1.008 (0.957–1.061)
NO ₂ (ppb)	0.947 (0.893–1.004)	1.004 (0.939–1.072)	1.031 (0.969–1.098)	1.014 (0.959–1.072)	0.926 (0.860–0.996)	0.929 (0.848–1.018)	1.003 (0.932–1.080)	0.97 (0.903–1.042)

Note: The values given in bold were statistically significant at the significance level of 0.05.

^aThe results of multi-pollutant model 1 were obtained from all nonsmokers' data including all variables above.

^bThe results of multi-pollutant model 2 were obtained from nonsmokers excluding those whose skin-prick test results were positive for DF or DP.

effects of exposure to SO₂ and cold temperatures on RA exacerbation. Our results are indirectly corroborated by those of Rabinovitch *et al.* (38), who report that passive smoking modifies the impact of exposure to air pollution on respiratory health. Furthermore, smokers with asthma exhibit greater reductions in lung function (39) and response to treatment with inhaled corticosteroids (40). Therefore, our results highlight the importance of accounting for smoking status when evaluating the impact of exposure to air pollution on asthma exacerbation.

In this study, we also found that the association between exposure to high SO₂ levels and the incidence of RA exacerbation was statistically significant in winter. Moreover, the median SO₂ concentration on the day of admittance in winter (9.3 ppb) was 31–82% higher than those of other seasons (7.1, 5.1, and 5.8 ppb in spring, summer, and winter, respectively). SO₂ is generated from vehicle exhaust and unrefined sulfur in anthracite. Our study area is located near the ocean and has a large volume of marine traffic nearby and numerous oil refineries. Furthermore, briquette, which is still used for heating low socioeconomic status households in the study area, might be another source of SO₂ exposure. Several studies show that living close to an oil refinery and using anthracite or biomass fuels are associated with an elevated incidence of airway inflammation (41–43). However, determining the exposure pathway and sources of SO₂ require further studies on exposure assessment.

We observed that approximately 41% of episodes (17 out of 41) occurred when the SO₂ concentration on Lag1 was significantly higher than that on control days and the temperature on Lag1 was significantly lower than that on corresponding control days (Supplementary Figure 1); similar results were obtained for Lag2 (data not shown). Further analysis using Spearman correlation tests revealed a weak correlation ($r = 0.225$, $p < .001$) between SO₂ concentration and temperature in winter. Interaction was not found between the two variables.

Although the median concentration of PM₁₀ on the day of Lag0 was significantly higher than that on control days in spring, springtime admissions due to RA exacerbation were not associated with PM₁₀ levels. One possible explanation for this finding is that RA patients may have taken precautionary measures. South Korea has yellow sand storms during the Asian dust period mostly during spring (March to May) but sometimes in fall (September to November) that causes very high PM₁₀ concentrations. Because RA patients might avoid outdoor activities in the presence of a known environmental threat such as yellow sand storms, hospital admissions due to RA exacerbations may not have increased significantly.

The strength of this study is the use of a case-crossover design, which minimizes the influence of confounding variables constant within each subject during the relevant time period, such as gender, secondhand smoke exposure, occupational exposure, and genetics (44). Furthermore, we controlled for the effects of allergen sensitization, smoking, and season by stratifying our dataset. However, this study has some limitations as well. First, rather than a

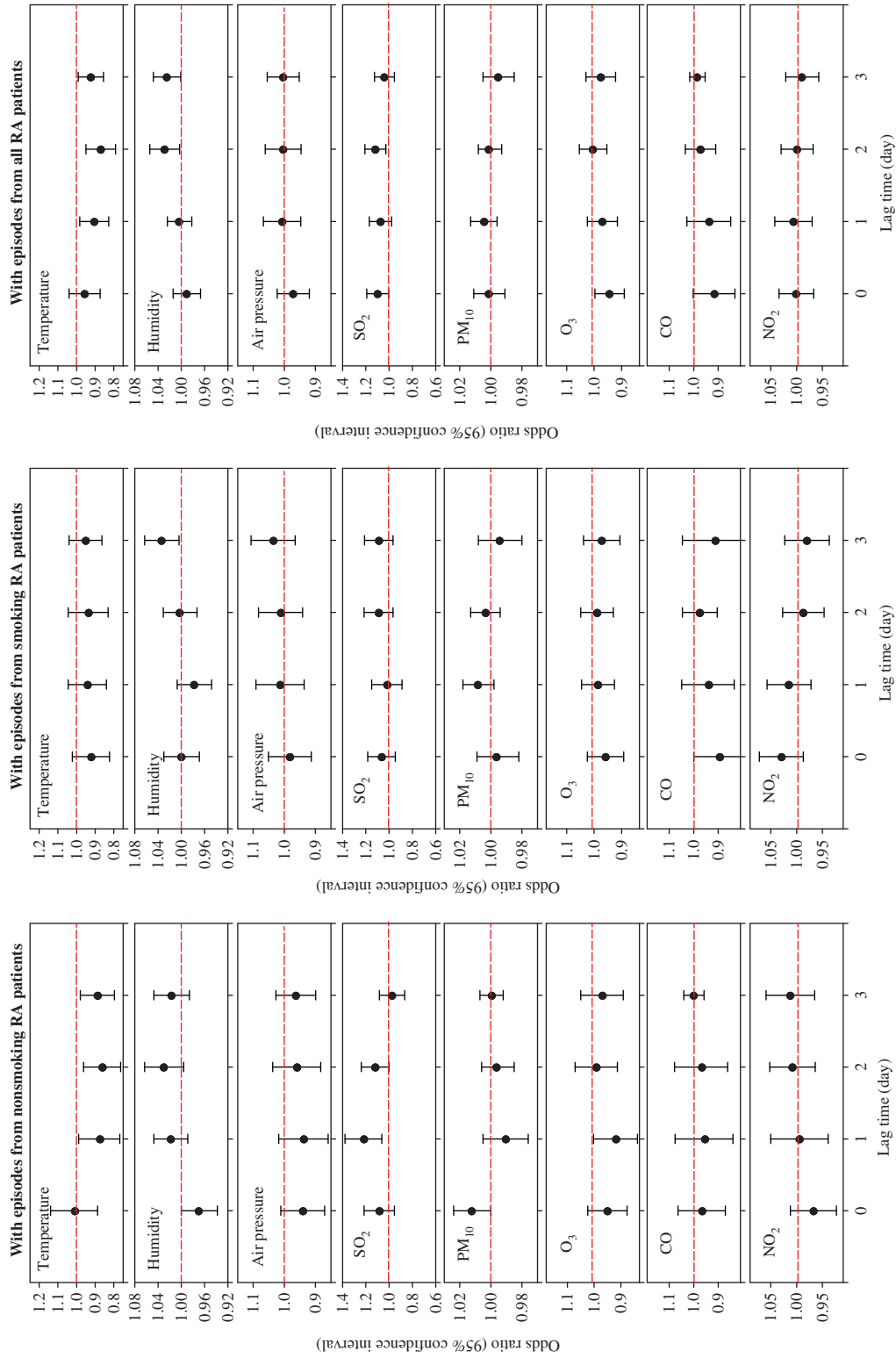


FIGURE 1.—Effects of air pollution and meteorological conditions on the risk of RA exacerbation in winter.

nationwide population sample, this study was conducted using a relatively small number of asthma patients from only three tertiary hospitals. Owing to the low frequency of RA (3.6% in our study), the recruitment of a sufficiently large cohort would require more time and money. A future study involving a larger sample size may increase statistical power. Second, due to the lack of information on viral infections and upper respiratory infections for the study population recruited from 2005 to 2009, we were unable to evaluate their impacts on asthma exacerbation. Therefore, future studies should consider expanding the data analysis by including information for viral infections or upper respiratory infections in RA patients. Third, we used only outdoor measurements of air pollutants and weather conditions. As individuals spend most of their time indoors, changes in indoor environments may contribute significantly to an increased risk of RA exacerbation. Indoor and/or occupational exposure levels and the duration of exposure during the time around each admission should be studied for the sake of accuracy. Finally, our study did not determine the degree of severity of the exacerbation. Further investigations of these variables will help clarify the factors involved in RA exacerbation.

CONCLUSION

Although our results must be interpreted carefully, our study is one of the few that reports the prevalence of RA (approximately 4%) among patients in an asthma cohort. Moreover, we examined the environmental factors determining RA exacerbation in nonsmoking adult patients after controlling for the effects of seasonality and sensitivity on common allergens. The results show that in winter, the occurrence of acute RA exacerbations is associated with exposure to temperature drops and increased SO₂ levels. Careful monitoring of temperature drops and SO₂ levels in winter will be beneficial for nonsmoking RA patients since these two factors may be markers that predict the occurrence of acute RA exacerbations with 1 or 2 day lags.

ACKNOWLEDGMENTS

We thank participating patients. We also thank the directors and staff of the Genome Research Center for Allergy and Respiratory Diseases, Soonchunhyang University Bucheon Hospital, South Korea.

FUNDING

This research was supported by the Korea Health Industry Development Institute, South Korea (#A090548).

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Global Initiative for Asthma. GINA Report: global strategy for asthma management and prevention 2011 May 4. Available at: http://www.ginasthma.org/uploads/users/files/GINA_Report2011_May4.pdf. Accessed April 25, 2012.
2. Green RH, Brightling CE, Bradding P. The reclassification of asthma based on subphenotypes. *Curr Opin Allergy Clin Immunol* 2007; 7(1):43–50.
3. American Thoracic Society. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000; 162(6):2341–2351.
4. Weiss KB, Gergen PJ, Wagener DK. Breathing better or wheezing worse? The changing epidemiology of asthma morbidity and mortality. *Annu Rev Public Health* 1993; 14:491–513.
5. Boutin-Forzano S, Adel N, Gratecos L, Jullian H, Garnier JM, Ramadour M, Lanteaume A, Hamon M, Lafay V, Charpin D. Visits to the emergency room for asthma attacks and short-term variations in air pollution: a case-crossover study. *Respiration* 2004; 71(2):134–137.
6. Fusco D, Forastiere F, Michelozzi P, Spadea T, Ostro B, Arca M, Perucci CA. Air pollution and hospital admissions for respiratory conditions in Rome, Italy. *Eur Respir J* 2001; 17(6):1143–1150.
7. Lavigne E, Villeneuve PJ, Cakmak S. Air pollution and emergency department visits for asthma in Windsor, Canada. *Can J Public Health* 2012; 103(1):4–8.
8. Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Scheike T, Loft S. Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. *J Expo Sci Environ Epidemiol* 2007; 17(7):625–636.
9. Sinclair AH, Edgerton ES, Wyzga R, Tolsma D. A two-time-period comparison of the effects of ambient air pollution on outpatient visits for acute respiratory illnesses. *J Air Waste Manag Assoc* 2010; 60(2): 163–175.
10. Mar TF, Koenig JQ. Relationship between visits to emergency departments for asthma and ozone exposure in greater Seattle, Washington. *Ann Allergy Asthma Immunol* 2009; 103(6):474–479.
11. Meng YY, Rull RP, Wilhelm M, Lombardi C, Balmes J, Ritz B. Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. *J Epidemiol Community Health* 2010; 64(2):142–147.
12. Berktaş BM, Bircan A. Effects of atmospheric sulphur dioxide and particulate matter concentrations on emergency room admissions due to asthma in Ankara. *Tuberk Toraks* 2003; 51(3):231–238.
13. Liu L, Poon R, Chen L, Frescura AM, Montuschi P, Ciabattini G, Wheeler A, Dales R. Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. *Environ Health Perspect* 2009; 117(4):668–674.
14. Nordling E, Berglund N, Melen E, Emenius G, Hallberg J, Nyberg F, Pershagen G, Svartengren M, Wickman M, Bellander T. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology* 2008; 19(3):401–408.
15. Mar TF, Koenig JQ, Primomo J. Associations between asthma emergency visits and particulate matter sources, including diesel emissions from stationary generators in Tacoma, Washington. *Inhal Toxicol* 2010; 22(6):445–448.
16. Villeneuve PJ, Chen L, Rowe BH, Coates F. Outdoor air pollution and emergency department visits for asthma among children and adults: a case-crossover study in northern Alberta, Canada. *Environ Health* 2007; 6:40.
17. Langdeau JB, Boulet LP. Prevalence and mechanisms of development of asthma and airway hyperresponsiveness in athletes. *Sports Med* 2001; 31(8):601–616.
18. Litonjua AA. Childhood asthma may be a consequence of vitamin D deficiency. *Curr Opin Allergy Clin Immunol* 2009; 9(3):202–207.
19. Varraso R. Nutrition and asthma. *Curr Allergy Asthma Rep* 2012; 12(3):201–210.
20. Martin JG, Siddiqui S, Hassan M. Immune responses to viral infections: relevance for asthma. *Paediatr Respir Rev* 2006; 7(Suppl. 1): S125–S127.

21. McHugh BM, MacGinnitie AJ. Indoor allergen sensitization and the risk of asthma and eczema in children in Pittsburgh. *Allergy Asthma Proc* 2011; 32(5):372–376.
22. Kent BD, Sulaiman I, Nicholson TT, Lane SJ, Moloney ED. Acute pulmonary admissions following implementation of a national workplace smoking ban. *Chest* 2012 Mar 1. [Epub ahead of print] doi: 10.1378/chest.11-2757, PMID: 22383660.
23. Hong YC, Pan XC, Kim SY, Park K, Park EJ, Jin X, Yi SM, Kim YH, Park CH, Song S, Kim H. Asian dust storm and pulmonary function of school children in Seoul. *Sci Total Environ* 2010; 408(4):754–759.
24. Lee JT, Son JY, Cho YS. A comparison of mortality related to urban air particles between periods with Asian dust days and without Asian dust days in Seoul, Korea, 2000–2004. *Environ Res* 2007; 105(3):409–413.
25. May L, Carim M, Yadav K. Adult asthma exacerbations and environmental triggers: a retrospective review of ED visits using an electronic medical record. *Am J Emerg Med* 2011; 29(9):1074–1082.
26. Min JY, Min KB, Cho SI, Paek D. Lag effect of particulate air pollution on lung function in children. *Pediatr Pulmonol* 2008; 43(5):476–480.
27. Barnes PJ, Woolcock AJ. Difficult asthma. *Eur Respir J* 1998; 12(5):1209–1218.
28. Saglani S, McKenzie SA. Environmental factors relevant to difficult asthma. *Paediatr Respir Rev* 2002; 3(3):248–254.
29. The ENFUMOSA study group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma: European network for understanding mechanisms of severe asthma. *Eur Respir J* 2003; 22(3):470–477.
30. Intergovernmental Panel on Climate Change. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge, UK: Cambridge University, 2007.
31. Tramuto F, Cusimano R, Cerame G, Vultaggio M, Calamusa G, Maida CM, Vitale F. Urban air pollution and emergency room admissions for respiratory symptoms: a case-crossover study in Palermo, Italy. *Environ Health* 2011; 10:31.
32. Lee JT, Kim H, Schwartz J. Bidirectional case-crossover studies of air pollution: bias from skewed and incomplete waves. *Environ Health Perspect* 2000; 108(12):1107–1111.
33. Bhaskaran K, Hajat S, Armstrong B, Haines A, Herrett E, Wilkinson P, Smeeth L. The effects of hourly differences in air pollution on the risk of myocardial infarction: case crossover analysis of the MINAP database. *BMJ* 2011; 343:d5531.
34. Nakaji S, Parodi S, Fontana V, Umeda T, Suzuki K, Sakamoto J, Fukuda S, Wada S, Sugawara K. Seasonal changes in mortality rates from main causes of death in Japan (1970–1999). *Eur J Epidemiol* 2004; 19(10):905–913.
35. Kaminsky DA, Bates JH, Irvin CG. Effects of cool, dry air stimulation on peripheral lung mechanics in asthma. *Am J Respir Crit Care Med* 2000; 162(1):179–186.
36. Abe T, Tokuda Y, Ohde S, Ishimatsu S, Nakamura T, Birrer RB. The relationship of short-term air pollution and weather to ED visits for asthma in Japan. *Am J Emerg Med* 2009; 27(2):153–159.
37. McDonald JS, Nelson J, Lenner KA, McLane ML, McFadden Jr ER. Effects of the combination of skin cooling and hyperpnea of frigid air in asthmatic and normal subjects. *J Appl Physiol* 1997; 82(2):453–459.
38. Rabinovitch N, Silveira L, Gelfand EW, Strand M. The response of children with asthma to ambient particulate is modified by tobacco smoke exposure. *Am J Respir Crit Care Med* 2011; 184(12):1350–1357.
39. James AL, Palmer LJ, Kicic E, Maxwell PS, Lagan SE, Ryan GF, Musk AW. Decline in lung function in the Busselton Health Study: the effects of asthma and cigarette smoking. *Am J Respir Crit Care Med* 2005; 171(2):109–114.
40. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. *Thorax* 2002; 57(3):226–230.
41. Albalak R, Frisano AR, Keeler GJ. Domestic biomass fuel combustion and chronic bronchitis in two rural Bolivian villages. *Thorax* 1999; 54(11):1004–1008.
42. Pandey MR. Domestic smoke pollution and chronic bronchitis in a rural community of the Hill Region of Nepal. *Thorax* 1984; 39(5):337–339.
43. Smargiassi A, Kosatsky T, Hicks J, Plante C, Armstrong B, Villeneuve PJ, Goudreau S. Risk of asthmatic episodes in children exposed to sulfur dioxide stack emissions from a refinery point source in Montreal, Canada. *Environ Health Perspect* 2009; 117(4):653–659.
44. Carracedo-Martinez E, Taracido M, Tobias A, Saez M, Figueiras A. Case-crossover analysis of air pollution health effects: a systematic review of methodology and application. *Environ Health Perspect* 2010; 118(8):1173–1182.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.