Short-term effects of multiple outdoor environmental factors on risk of asthma exacerbations: Age-stratified time-series analysis

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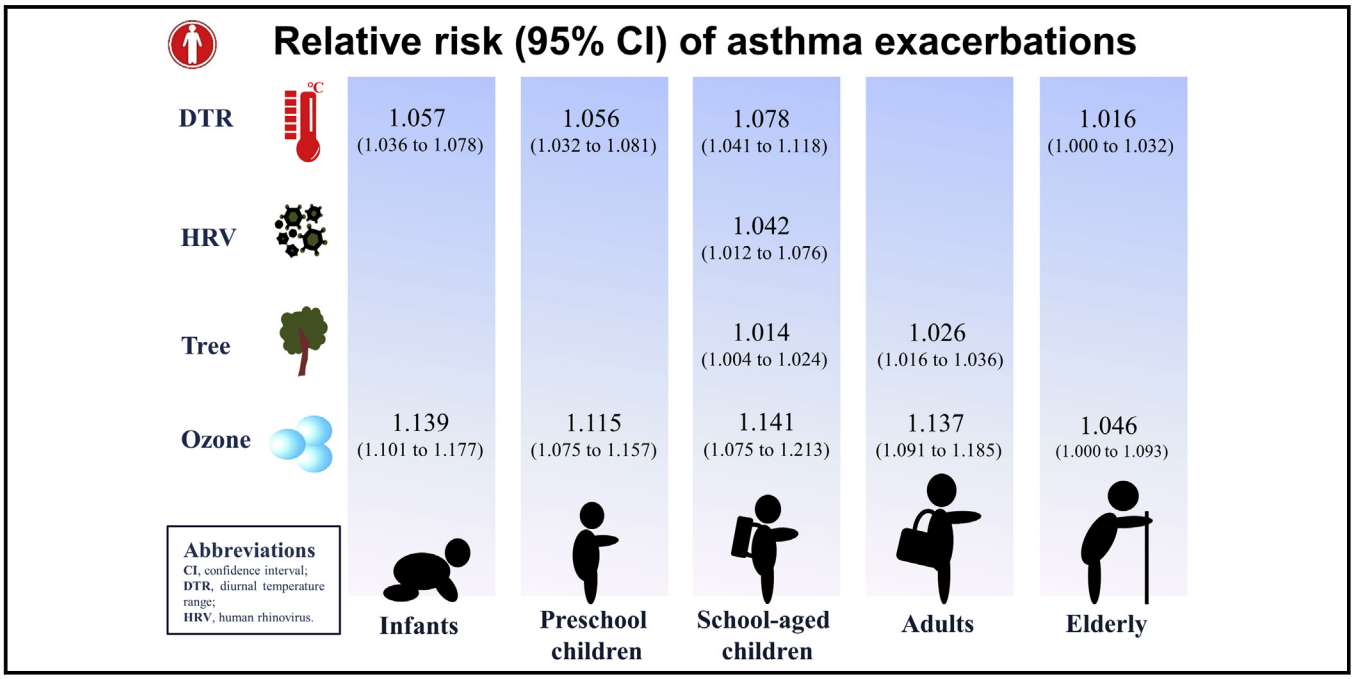
GRAPHICAL ABSTRACT



Background: Although the different age groups had differences in sensitivity of asthma exacerbations (AEs) to environmental factors, no comprehensive study has examined the age-stratified effects of environmental factors on AEs.

Objective: We sought to examine the short-term effects in age-stratified groups (infants, preschool children, school-aged children, adults, and the elderly) of outdoor environmental factors (air pollutants, weather conditions, aeroallergens, and respiratory viral epidemics) on AEs.

Methods: We performed an age-stratified analysis of the short-term effects of 4 groups of outdoor environmental factors on AEs in Seoul Metropolitan City (Korea) from 2008 and 2012. The statistical analysis used a Poisson generalized linear regression model, with a distributed lag nonlinear model for identification of lagged and nonlinear effects and convergent cross-mapping for identification of causal associations.

Results: Analysis of the total population (n = 10,233,519) indicated there were 28,824 AE events requiring admission to an

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emergency department during the study period. Diurnal temperature range had significant effects in pediatric (infants, preschool children, and school-aged children) and elderly (relative risk [RR], 1.056-1.078 and 1.016, respectively) subjects. Tree and weed pollen, human rhinovirus, and influenza virus had significant effects in school-aged children (RR, 1.014, 1.040, 1.042, and 1.038, respectively). Tree pollen and influenza virus had significant effects in adults (RR, 1.026 and 1.044, respectively). Outdoor air pollutants (particulate matter of ≤10 μm in diameter, nitrogen dioxide, ozone, carbon monoxide, and sulfur dioxide) had significant short-term effects in all age groups (except for carbon monoxide and sulfur dioxide in infants).

Conclusion: These findings provide a need for the development of tailored strategies to prevent AE events in different age groups. (J Allergy Clin Immunol 2019;144:1542-50.)

Key words: *Asthma exacerbation, air pollutant, weather condition, aeroallergen, human rhinovirus, influenza virus*

Asthma exacerbations (AEs) are especially common in young and elderly subjects[1] and are associated with seasonal variations of environmental factors, such as weather conditions, aeroallergens, and ambient air pollution.[2] There is an autumnal peak of AEs in children caused by human rhinovirus (HRV) and a winter peak in elderly subjects from the United States[3] and Korea[4,5] caused by the influenza virus (IFV). Ambient air pollutants,[6-8] aeroallergens,[9] and certain weather conditions.[5,10,11] can exacerbate the effects of these viral respiratory tract infections.[2] Furthermore, AEs are more common in infants[11-13] and the elderly[14] after exposure to air pollutants and changes in weather.

Although previous studies have identified individual factors associated with the risk of AEs,[2,5-11,15] no comprehensive study has examined the effects of all these factors on AEs. Thus we comprehensively examined the short-term effects of multiple environmental factors (air pollutants, weather conditions, aeroallergens, and burden of viral respiratory tract infections) on AEs in an age-stratified population from Seoul Metropolitan City in an effort to develop effective personalized strategies for prevention of AEs.

METHODS

Study population

This time-series analysis was a retrospective population-based cohort study in Seoul Metropolitan City (Republic of Korea) from January 2008 to December 2012. Data are from the registries of 257 hospitals in Seoul and were extracted from the National Health Insurance System of the Health Insurance Review and Assessment Service, which covers approximately 98% of the Korean population.[16] These records have patient information (age and sex), date of visit, and disease diagnosis based on the International Classification of Diseases, 10th revision (ICD-10). Detailed descriptions of these data were provided previously.[4]

The database included all AE events requiring admission to an emergency department that were coded by ICD-10 as J45 (asthma) or J46 (status asthmaticus).[17] Subjects were classified into 5 age groups: younger than 2 years (infants), 2 to 5 years (preschool children), 6 to 17 years (school-aged children), 18 to 59 years (adults), and 60 years or older (elderly). This research was approved by the appropriate Institutional Review Board of CHA University (2017-03-007).

Abbreviations used

AE: Asthma exacerbation
CO: Carbon monoxide
DLNM: Distributed lag nonlinear model
DTR: Diurnal temperature range
HRV: Human rhinovirus
ICD-10: International Classification of Diseases, 10th revision
IFV: Influenza virus
NO_2: Nitrogen dioxide
O_3: Ozone
PM_{10}: Particulate matter of 10 μm or less in diameter
RR: Relative risk
RSV: Respiratory syncytial virus
SO_2: Sulfur dioxide
SS: Solar sunshine hours

Outdoor air pollutants, weather conditions, outdoor aeroallergens, and burden of viral respiratory tract infections

Table I lists the multiple items in 4 major categories that could affect AE: outdoor air pollutants, weather conditions, outdoor aeroallergens, and burden of viral respiratory tract infections. Data on air pollutants were from the Ministry of the Environment (Korean government); daily mean concentrations were recorded at 34 observatory stations in Seoul, and daily average values were calculated for each air pollutant. Data on meteorological factors in Seoul (latitude, 37.57° N) were from the Korea Meteorological Administration. Outdoor aeroallergen concentrations were from the Asian-Pacific Pollen Allergy Network; daily counts of tree, grass, and weed pollens were recorded from 3 pollen-collecting station in Seoul[18] using 7-day recording volumetric spore traps (Burkard Manufacturing, Rickmansworth, United Kingdom). Weekly nationwide viral respiratory tract detection rates were calculated from the results of respiratory virus PCR from the Korea Centers for Disease Control and Prevention.[4]

Statistical analysis

A Poisson generalized linear regression model combined with a distributed lag nonlinear model (DLNM) was used to determine lagged and nonlinear effects and to quantify the effect of environmental variables (daily outdoor air pollutants, daily weather conditions, daily outdoor aeroallergens, and 7-day moving average of nationwide viral respiratory tract detection rate) on AE.[19] For all variables, 0 to 4 lag days had the maximum relative risk (RR); after lag day 6, the RR was approximately 1, and the RR was not statistically significant after lag day 7. Therefore the multivariable DLNM for pollutants is as follows:

$$\log E(Y_t) = \sum_{l=1}^{7}[\beta_l Z_{t-l}] + DOW + PubH + ns(Time,\ 4df/year) + ns(HM,\ 5\ df) + ns(SS,\ 8\ df) + ns(DTR,\ 7\ df) + ns(tree,\ 8\ df) + ns(grass,\ 3\ df) + ns(weed,\ 8\ df) + ns(HRV,\ 9\ df) + ns(IFV,\ 6\ df) + ns(RSV,\ 7\ df) + Lag(res,\ 1),$$

where $E(Y_t)$ is the number of daily AE events expected on day t; β_l is the log relative rate coefficients for lag l; Z_{t-l} is each independent variable for day t at lag l; day of the week *(DOW)* and public holidays *(PubH)* are controlled categorical variables; *ns(Time, 4 df/year)* is the natural cubic spline function *(ns)* for time, with 4 *df*/y selected by calculating the minimum of the residuals using the partial autocorrelation function[13] (*df* was selected based on the lowest Akaike information criterion[10]); and *Lag(res, 1)* is the DLNM model residual error of the first-order lagged variable to control the autocorrelation function and control for seasonality and long-term trends in AEs. If the associations tended to be linear in the single DLNM model, we used a linear function; if not, we used a natural cubic spline function.

TABLE I. Outdoor environmental variables that potentially affect AE events, data sources, and summary statistics for Seoul Metropolitan City from 2008 to 2012

Variable	Data source	Summary statistics	
Outdoor air pollutants	Ministry of Environment, Korea government	Daily median (IQR)	
PM_{10} ($\mu g/m^3$)		43.97 (30.35-58.56)	
NO_2 (ppm)		0.0352 (0.0272-0.0447)	
O_3 (ppm)		0.0170 (0.0101-0.0244)	
CO (ppm)		0.548 (0.452-0.680)	
SO_2 (ppm)		0.00491 (0.00394-0.00632)	
Weather condition	Korea Meteorological Administration	Daily median (IQR)	
Humidity (%)		60.1 (48.6-71)	
Solar sunshine (h)		6.6 (1.7-9.1)	
DTR (°C)		8.1 (6.2-9.9)	
Outdoor aeroallergens	Asian-Pacific Pollen Allergy Network	Daily mean (range)	Daily median (IQR)
Tree (grains/m^3)		35.7 (0-2716)	0 (0-4)
Grass (grains/m^3)		0.446 (0-18)	0 (0-1)
Weed (grains/m^3)		9.11 (0-1086)	0 (0-1)
Burden of viral respiratory tract infections	Korea Centers for Disease Control and Prevention	Seven-day moving average (IQR)	
HRV, positive rate (%)		8.40 (5.08-12.50)	
IFV, positive rate (%)		1.22 (0.00-7.84)	
RSV, positive rate (%)		1.42 (0.41-3.42)	

IQR, Interquartile range.

For other variables, such as weather, the term $\sum_{l=1}^{7}\beta_l Z_{t-1}$ now changes according to each weather condition variable, such as humidity, solar sunshine hours (SS), and diurnal temperature range (DTR). In this case line 2 (weather confounder) changes to pollutants, which is then a confounder. The exact *df* values were 3 for particulate matter of 10 μm or less in diameter (PM_{10}), 2 for nitrogen dioxide (NO_2), 2 for ozone (O_3), 3 for carbon monoxide (CO), and 2 for sulfur dioxide (SO_2). Therefore line 2 was changed to the following:

$$+ns(PM_{10}, 3\ df) + ns(NO_2, 2\ df) + ns(O_3, 2\ df) + ns(CO, 3\ df)$$
$$+ns(SO_2, 2\ df)$$

This modification was also implemented in the case of aeroallergens and viral respiratory tract infections.

Convergent cross-mapping is a nonparametric approach capable of identifying causality between 2 variables within the same nonlinear dynamic system.[20,21] For each pairwise interaction between environmental factors, we used convergent cross-mapping to test for causal interactions, assuming causality when the maximum cross-map skill was greater than 0.2 and the *P* value was less than .05. We used this approach to exclude confounding variables from our analysis, thereby reducing multicollinearity between independent variables in the final model.

The final model was retested, including validated AE events, and a sensitivity analysis was used to modify the *df* in the final model by varying the exposure response or single-lag model (changing the *df* [0-8] for time, humidity, SS, DTR, tree, grass, weed, HRV, IFV respiratory syncytial virus [RSV], PM_{10}, NO_2, O_3, CO, and SO_2 to evaluate the single-lag model and final DLNM model). Moreover, DLNM model residuals were time independent, with normal distribution and no apparent autocorrelation. After this sensitivity analysis, the peak lag day remained the same and retained its statistical significance. Therefore our modeling was not affected by the choice of *df* and interactions with multiple outdoor environmental factors.

Interquartile ranges were used as reference ranges to calculate RRs in describing the dynamics of outdoor environmental factors in Seoul. However, the 100 or 1 grain/m^3 increments were used as reference ranges to calculate RRs of aeroallergens caused by overly large SDs. Data were analyzed with a Fourier regression model to characterize the seasonal dynamics of environmental changes.[4] All analyses were conducted with R software (version 3.5.1). A *P* value of less than .05 was considered statistically significant.

RESULTS

Baseline data

There were 10,233,519 subjects living in Seoul and 28,824 AE events (daily mean, 15.78 ± 7.78) between January 2008 and December 2012. A total of 2989 (10.37%) AE events were in infants: 5924 (20.55%) in preschool children, 4597 (15.95%) in school-aged children, 8639 (29.97%) in adults, and 6675 (23.16%) in the elderly (Fig 1, *A*). Further analysis indicated that male subjects had a greater incidence among patients younger than 20 years old and female subjects had a greater incidence among patients who were 20 to 50 years old (Fig 1, *B*).

Seasonal dynamics and convergent cross-mapping of AEs and outdoor environmental factors

We observed distinct seasonal changes of AE events in the different age groups (Fig 1, *C*). Thus in subjects younger than 60 years, there were dominant peaks during the spring and fall. The fall peak appeared more dominant in school-aged children and adults, whereas the spring peak appeared more dominant in infants and preschoolers. There appeared to only be a winter peak in the elderly. Outdoor air pollutants and weather variables had smooth cyclic patterns (Fig 1, *D* and *E*), whereas outdoor aeroallergens and burden of viral respiratory tract infection had sharp maxima and minima (Fig 1, *F* and *G*).

Using convergent cross-mapping, we found independent variables with possible causal associations (see Table E1 in this article's Online Repository at www.jacionline.org). For example,

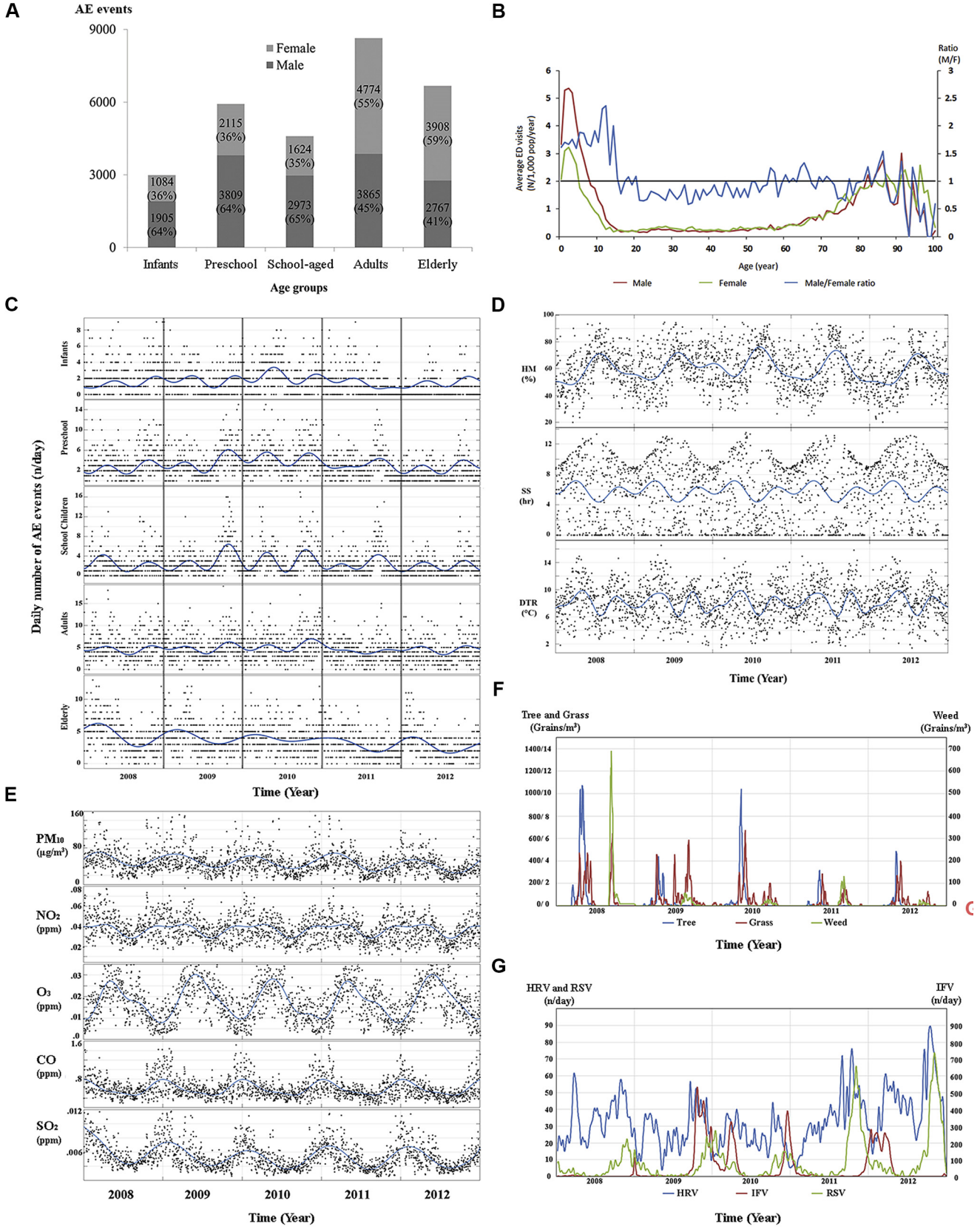

FIG 1. Seasonal dynamics of AEs, air pollutants, weather conditions, aeroallergens, and burden of viral respiratory tract infections from 2008 to 2012. **A,** Total AE events in different age groups. **B,** Yearly average AE events per 1000 persons. **C,** Seasonal dynamics of AE events in different age groups. **D,** Daily weather conditions. **E,** Daily concentrations of air pollutants. **F,** Daily levels of aeroallergens. **G,** Seven-day moving average levels of circulating viral respiratory tract infections. *Blue lines* indicate fits to a Fourier regression, and *black dots* indicate actual measurements (Fig 1, *C-E*).

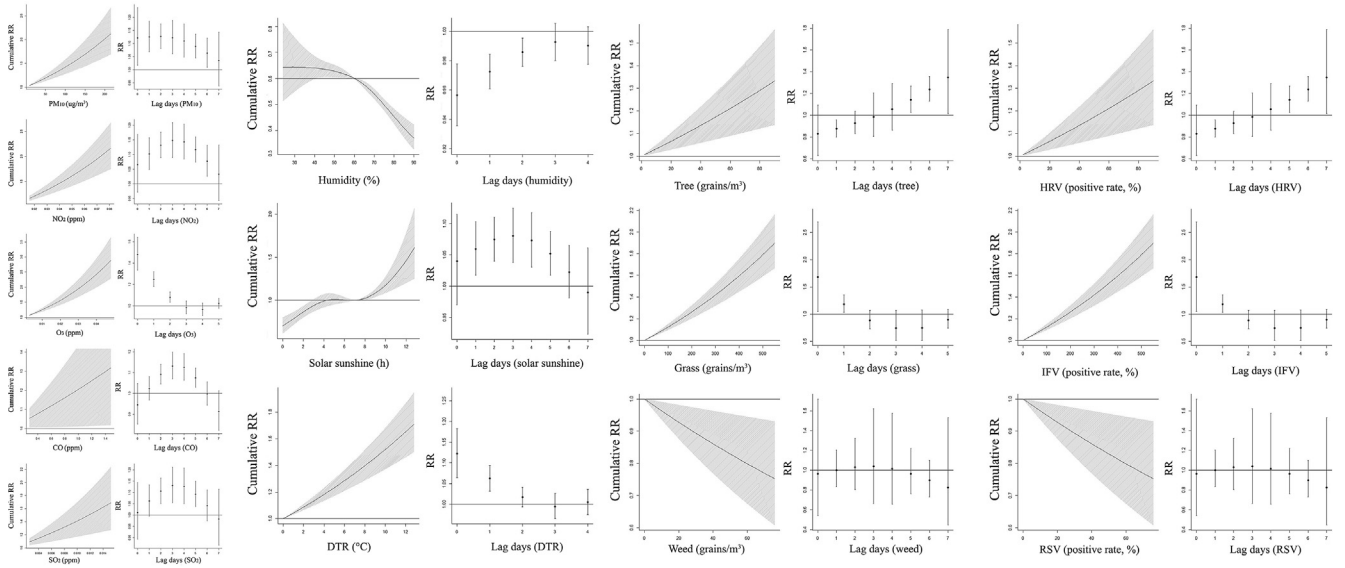

FIG 2. Estimated cumulative effect of outdoor environmental factors (air pollutants, weather conditions, aeroallergens, and burden of viral respiratory tract infections) on AE events *(left panels)* and RRs of outdoor environmental factors with different lag days on AE events *(right panels)*. Data are shown as 95% CIs. *IQR*, Interquartile range. *Lag day 0*, Current day; *Lag day 1*, 1 day previously; *Lag day 2*, 2 days previously; *Lag day 3*, 3 days previously; and *Lag day 4*, 4 days previously.

DTR and O_3 each showed a significant maximum cross-map skill value with tree aeroallergens. Thus when testing the RRs of tree aeroallergens, we excluded DTR and O_3 from the model.

Estimated cumulative and lag time effects of outdoor environmental factors on AE events

Our results indicated the presence of cumulative and lag time effects for all 5 outdoor air pollutants, weather conditions, outdoor aeroallergens, and burden of viral respiratory tract infections (Fig 2). The estimated RR of AE events was nonlinearly associated with humidity and SS and positively associated with the 5 air pollutants (PM_{10}, NO_2, O_3, CO, and SO_2), DTR, 2 aeroallergens (tree and grass pollens), HRV, and IFV. The peak effects of PM_{10}, NO_2, CO, and SO_2 were on lag day 2 or 3 and remained statistically significant until lag day 5 or 6; O_3 had a short-term effect (peak effect on lag day 0) and became insignificant on lag day 3. In contrast, DTR, tree pollen, and IFV mostly had more rapid effects (peak effect on lag day 0). Moreover, the peak lag day was 2 for grass pollen and 7 for HRV. None of the RRs for lag effect of weed pollen or RSV on AE events were significant.

Estimated RRs of environmental factors on AE events stratified by age

The estimated RR interquartile range from the final model indicated that AE events were associated with O_3, DTR, and tree pollen on lag day 0; with PM_{10}, NO_2, CO, and IFV on lag day 3; and with SO_2 and weed pollen on lag day 5 (Fig 3). The final model indicated no evidence for significant effects of humidity, SS, grass pollen, HRV, and RSV. However, HRV was significantly associated with AE events in school-aged children (Table II) in contrast to the results of the final overall model.

Analysis of age-stratified results indicated that infants had an increased risk of AE events from PM_{10}, NO_2, O_3, and DTR on lag day 0 (Table II). Preschool children had an increased risk of AE events from all 5 air pollutants and DTR on lag day 0 or 3. School-aged children had an increased risk of AE events from all 5 air pollutants, as well as tree and weed pollen, HRV, and IFV, on lag day 5. Adults had an increased risk of AE events from all 5 air pollutants, tree pollen, and IFV on lag day 0, 3, or 4. The elderly had an increased risk of AE events from all 5 air pollutants and DTR on lag day 6.

DISCUSSION

Key results

To the best of our knowledge, this is the first comprehensive age-stratified time-series analysis to identify the short-term effects of outdoor environmental factors (air pollutants, weather conditions, aeroallergens, and burden of viral respiratory tract infections) on AE events in Korea. In general, our results indicate that the different age groups had differences in their sensitivity to the different environmental factors, that PM_{10} had the greatest effect on AE events, and that these effects were greatest and almost immediate (lag day 0) in infants but tended to decrease with patient age. The effects of NO_2, O_3, CO, SO_2, DTR, HRV infections, and weed aeroallergens were greatest in school-aged children. All 5 air pollutants, tree aeroallergens, and IFV infection had significant associations with AE events in adults. DTR had a rapid effect in infants and children (lag day 0) but a more delayed effect in the elderly (lag day 6). These results suggest that strategies to prevent AEs should consider the patient's age and multiple environmental factors.

Outdoor air pollutants

Higher concentrations of outdoor air pollutants increased the RRs of AE events, although the strength of these effects varied among age groups. Our results confirmed that PM_{10} and NO_2 had significant short-term effects on AE events in infants (lag day 0) but more delayed effects in adults (lag day 3 or 4). This might be

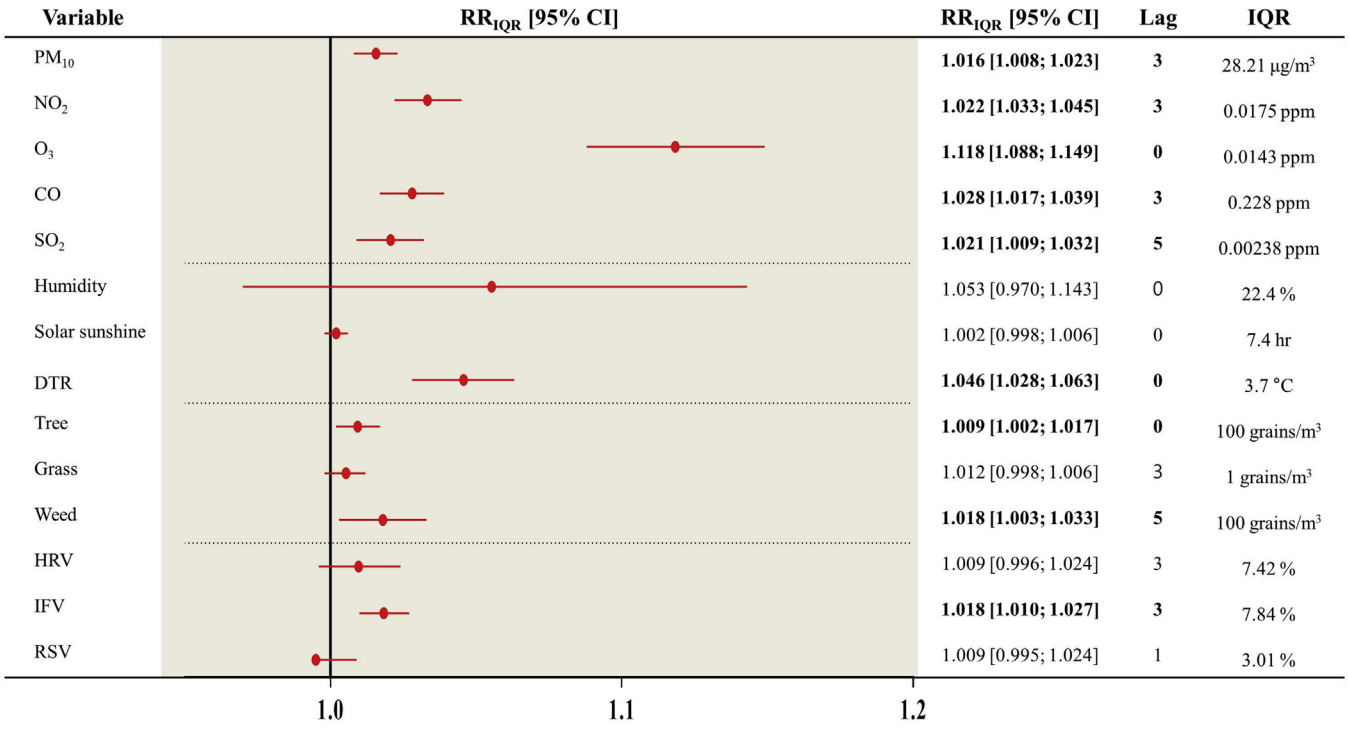

FIG 3. RRs of outdoor air pollutants, weather conditions, aeroallergens, and burden of viral respiratory tract infections on AE events estimated from the final model and adjusted for factors listed in Table II. *IQR*, Interquartile range. *Lag day 0*, Current day; *Lag day 1*, 1 day previously; *Lag day 2*, 2 days previously; *Lag day 3*, 3 days previously; and *Lag day 4*, 4 days previously.

because young children have underdeveloped immune systems and lungs and anatomically small peripheral airways, so that inflammation of their airways leads to more rapid and severe obstruction.[13] O_3 had the greatest effect in school-aged children, possibly because of the high ground-surface O_3 levels and significant outdoor activities of this age group.[22] The ground-surface O_3 level from 10 AM to 6 PM is generally greater than at other times of the day, and Korean school-aged children engage in more outdoor activities at these times.[22] Although we also found significant short-term effects of SO_2 and CO in some age groups, the significance of these factors on AEs remain controversial. A recent meta-analysis of 87 studies reported that short-term exposures to air pollutants (PM_{10}, NO_2, O_3, CO, and SO_2) were associated with increased risk of emergency department visits and hospital admissions for asthma.[8] However, another multilevel meta-analysis of 22 studies on AEs reported no association of SO_2 overall and no effect of CO in children.[7]

PM generated from traffic and transportation might contribute to oxidative stress, airway hyperresponsiveness and remodeling, and allergic sensitization with T_H2 and T_H17 phenotype differentiation.[6-8] The main gases that trigger AEs[6-8] are NO_2 (main source: fossil fuel combustion in urban environments; mechanism: bronchial inflammation), O_3 (main source: secondary pollutant generated by photochemical reactions, mechanism: airway hyperresponsiveness and inflammation and decreased lung function), and SO_2 (main source: industrial processes in developed regions, mechanism: bronchoconstriction).

In addition, previous research indicated pollutant concentration, and the RRs of AEs are linearly related at all measured concentrations, even very low ones. In other words, there is no completely safe lower threshold for air pollutants.[6-8] This is consistent with our findings. Our identification of the significant effects of outdoor air pollution on AE events suggests that preventive strategies for these factors should focus on school-aged children and infants.

Weather conditions

We found that a large DTR had a significant effect on AEs in infants, children, and the elderly. Previous studies have also identified a link between asthma and large DTRs in pediatric patients[5,10,11] but not the elderly. Sudden changes in temperature within 1 day can lead to mast cell–mediated release of inflammatory factors and an inflammatory nasal response,[23] and this might explain the increased vulnerability in the elderly and children.[5,10,11] Thus strategies that prevent the elderly and children from being exposed to large temperature changes might help reduce the number of AEs.

It is uncertain whether the effect of humidity on AEs is direct or indirect (because humidity is related to aeroallergen and air pollutant levels).[24] Several studies showed that AE events were directly associated with high humidity,[11,13,25] but another study showed that AE events were associated with low humidity.[26] Our results showed that humidity had a significant effect on AEs in the single model but not in the final model. Thus we cannot confirm a direct effect of humidity on AEs.

Outdoor aeroallergens and viral respiratory tract infection epidemics

Tree aeroallergens had no effect on AEs in infants and preschoolers. This is likely because infants tend to be more

TABLE II. Age-stratified RRs of air pollutants, weather conditions, aeroallergens, and burden of viral respiratory tract infections on AE events

		Infants		Preschool children		School-aged children		Adults		Elderly	
Variables	**Increment**	**RR* (95% CI)**	**Lag†**	**RR (95% CI)**	**Lag**	**RR (95% CI)**	**Lag**	**RR (95% CI)**	**Lag**	**RR (95% CI)**	**Lag**
Air pollutants											
PM_{10}‡	28.21 μg/m^3	**1.031 (1.014-1.048)**	**0**	**1.024 (1.004-1.043)**	**0**	**1.020 (1.008-1.032)**	**3**	**1.020 (1.008-1.032)**	**3**	**1.010 (1.001-1.019)**	**2**
NO_2§	0.0175 ppm	**1.035 (1.009-1.061)**	**0**	**1.024 (1.007-1.041)**	**3**	**1.046 (1.020-1.072)**	**3**	**1.034 (1.017-1.052)**	**4**	**1.027 (1.009-1.046)**	**3**
O_3‖	00.0143 ppm	**1.139 (1.101-1.177)**	**0**	**1.115 (1.075-1.157)**	**0**	**1.141 (1.075-1.213)**	**0**	**1.137 (1.091-1.185)**	**0**	**1.046 (1.000-1.093)**	**0**
CO¶	0.228 ppm	1.007 (0.995-1.020)	3	**1.019 (1.004-1.035)**	**4**	**1.037 (1.012-1.063)**	**4**	**1.035 (1.019-1.051)**	**4**	**1.027 (1.010-1.044)**	**3**
SO_2¶	0.00238 ppm	1.003 (0.989-1.017)	5	**1.022 (1.004-1.039)**	**4**	**1.028 (1.001-1.055)**	**4**	**1.021 (1.004-1.038)**	**4**	**1.028 (1.012-1.046)**	**4**
Weather condition											
Humidity#	22.4%	0.963 (0.904-1.026)	4	1.045 (0.969-1.127)	4	1.122 (0.935-1.345)	0	1.051 (0.933-1.184)	0	1.138 (1.004-1.290)	0
Solar sunshine**	7.4 h	1.002 (0.997-1.006)	0	1.003 (0.998-1.009)	0	0.998 (0.990-1.007)	0	1.003 (0.996-1.009)	0	1.003 (0.996-1.009)	0
DTR††	3.7°C	**1.057 (1.036-1.078)**	**0**	**1.056 (1.032-1.081)**	**0**	**1.078 (1.041-1.118)**	**0**	1.013 (0.989-1.038)	7	**1.016 (1.000-1.032)**	**6**
Aeroallergen											
Tree‡‡	100 grains/m^3	1.005 (0.999-1.011)	1	1.005 (0.994-1.016)	0	**1.014 (1.004-1.024)**	**4**	**1.026 (1.016-1.036)**	**0**	1.005 (0.993-1.017)	0
Grass§§	1 grain/m^3	1.004 (0.999-1.009)	2	1.001 (0.995-1.006)	2	1.013 (0.997-1.030)	0	1.008 (0.996-1.020)	0	1.005 (0.998-1.012)	1
Weed‖‖	100 grains/m^3	1.024 (0.970-1.081)	7	1.015 (0.958-1.084)	0	**1.040 (1.009-1.072)**	**5**	1.027 (0.979-1.077)	7	1.045 (0.979-1.077)	7
Viral respiratory tract infection											
HRV¶¶	7.42%	1.005 (0.984-1.158)	0	1.018 (0.971-1.079)	0	**1.042 (1.012-1.076)**	**3**	1.009 (0.984-1.041)	0	1.006 (0.993-1.021)	3
IFV¶¶	7.84%	1.005 (0.990-1.024)	3	1.005 (0.992-1.019)	3	**1.038 (1.016-1.064)**	**3**	**1.044 (1.011-1.083)**	**0**	1.010 (0.994-1.030)	0
RSV##	3.01%	1.011 (0.933-1.134)	3	1.010 (0.994-1.029)	1	0.999 (0.997-1.005)	0	1.000 (1.000-1.001)	3	1.000 (1.000-1.000)	3

Values in boldface indicate statistically significant associations ($P < .05$).

DOW, Day of the week; *IQR*, interquartile range.

*Greatest RR in 7 lag days.

†*Lag day 0*, Current day; *Lag day 1*, 1 day previously; *Lag day 2*, 2 days previously; *Lag day 3*, 3 days previously; and *Lag day 4*, 4 days previously.

‡Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), residual error of first-order lagged variable, weather conditions (humidity, solar sunshine, and DTR), aeroallergens (tree, grass, and weed), and viral respiratory tract infections (HRV, IFV, and RSV).

§Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), residual error of first-order lagged variable, weather conditions (solar sunshine), aeroallergens (tree, grass, and weed), and viral respiratory tract infections (HRV, IFV, and RSV).

‖Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), residual error of first-order lagged variable, aeroallergens (weed), and viral respiratory tract infections (HRV, IFV, and RSV).

¶Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), residual error of first-order lagged variable, weather conditions (solar sunshine and DTR), aeroallergens (tree, grass, and weed), and viral respiratory tract infections (HRV, IFV, and RSV).

#Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}), aeroallergens (tree, grass, and weed), and viral respiratory tract infections (HRV, IFV, and RSV).

**Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, NO_2, CO, and SO_2), aeroallergens (tree, grass, and weed), and viral respiratory tract infections (HRV, IFV, and RSV).

††Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, CO, and SO_2), aeroallergens (grass and weed), and viral respiratory tract infections (HRV, IFV, and RSV).

‡‡Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, NO_2, CO, and SO_2), weather conditions (humidity, solar sunshine, and DTR), and viral respiratory tract infections (HRV and IFV).

§§Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, NO_2, CO, and SO_2), weather conditions (humidity, solar sunshine, and DTR), and viral respiratory tract infections (HRV, IFV, and RSV).

‖‖Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, NO_2, O_3, CO, and SO_2), weather conditions (humidity, solar sunshine, and DTR), and viral respiratory tract infections (HRV, IFV, and RSV).

¶¶Risk factors were adjusted for DOW, public holidays, *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, NO_2, O_3, CO, and SO_2), weather conditions (humidity, solar sunshine, and DTR), and aeroallergens (tree, grass, and weed).

##Risk factors were adjusted for DOW, public holidays, and *df* (to account for long-term and seasonal effects), air pollutants (PM_{10}, NO_2, O_3, CO, and SO_2), weather conditions (humidity, solar sunshine, and DTR), and aeroallergens (grass and weed).

sensitized to indoor allergens, such as house dust mites, than outdoor aeroallergens, and they become more sensitized to outdoor allergens as they grow older.[27]

Among the 3 aeroallergens we examined, weed allergens had significant effects on AE events in school-aged children, and tree allergens had significant effects on AE events in school-aged children and adults. Grass allergens had no effect on AE events in any age group. This might be because the concentration of grass aeroallergens is low in Korea, which is in contrast to the situation Europe.[18,28] A previous study reported that mold aeroallergens can also trigger AEs.[25] However, mold concentrations are too low for detection in Korea. Thus the presence and effect of aeroallergens on AEs vary among different countries, and therefore strategies to prevent AEs from aeroallergens should consider the specific conditions of each country.

It is well known that HRV infections are a main cause of AEs in school-aged children,[28] and this is consistent with our results. Moreover, IFV is often concurrent with AE events,[3] especially in older subjects.[4] However, we found that the effect of influenza on AEs was greatest in adults but not the elderly. This might be because the nationwide influenza vaccination program in Korea

targets the elderly. A recent study reported the vaccination rate was 76% for subjects older than 65 years, and the incidence rate of influenza-like illness is lower in the elderly than in adults.[29,30]

A synergistic interaction of respiratory tract viruses and allergens might exacerbate allergic inflammation, deficiencies in the epithelium, or the severity of viral infections.[31] Therefore prevention of respiratory tract infections through promotion of hand hygiene and vaccination might help prevent AEs.

Policy implications

Strategies for prevention of AEs should be tailored for different age groups. First, it is important to provide educational health messages regarding DTRs in pediatric and elderly persons, groups that are especially vulnerable to temperature changes. Second, for children and adults who engage in a lot of outdoor activities, strategies to prevent AEs should consider seasonal variations of aeroallergens. Third, school-aged children and adults who engage in community-based social activities should be alerted to the prevalence of viral respiratory tract infections, such as IFV and HRV. Finally, because there is no completely safe level of air pollutants, more stringent regulations on industry and automobiles and a more active notification system for high levels of air pollutants might help prevent AEs.

Strengths and limitations

There are major limitations to consider when interpreting our findings. Our results might have been affected by heterogeneous data-sampling strategies (air pollutants, weather conditions, outdoor aeroallergens, and burden of viral respiratory tract infections). The strongest relationships are seen with outdoor air pollutants, which were measured daily, whereas the weakest relationships are seen with viral data, which were collected weekly. In addition, aeroallergen exposure occurred only in 1 to 2 months of the year, although the normality of the residuals was confirmed for aeroallergen data. Another possible limitation is that we did not have information on allergic sensitization as an effect modifier of AE by interacting with multiple outdoor environmental factors.[31] Moreover, because we fitted a population-level model, we speculate that it is possible that virus surveillance, in particular, did not fully reflect personal exposure compared with the other outdoor environmental variables (ie, outdoor air pollutants, weather condition, and outdoor aeroallergens). We also only showed a short-term effect and adjusted for various outdoor environmental factors, including weather conditions, which might have resulted in the weaker association with virus surveillance than other outdoor environmental variables.

Second, because we used ICD codes to identify AEs, we might have inadvertently included some elderly patients who had chronic obstructive pulmonary disease and some infants and preschool children who had acute bronchiolitis. Moreover, we were not able to distinguish newly diagnosed asthma from chronic asthma. In addition, we did not examine subjects from rural areas or any long-term effects (after lag day 7).

Finally, we did not include non–emergency department visits and therefore were unable to consider subjects with mild AEs.

Despite these limitations, to the best of our knowledge, this is first large-scale study to examine the short-term effects of multiple outdoor environmental factors on AE events. Moreover, we investigated the entire population of Seoul Metropolitan City, and our research design allowed us to examine the effects of multiple outdoor environmental factors on different age groups.

Conclusions

In conclusion, we examined the short-term effects of air pollutants, DTR, aeroallergens, and burden of IFV and HRV on AEs in different age groups in Seoul, Korea. We found that multiple outdoor environmental factors (outdoor air pollutants, weather conditions, outdoor aeroallergens, and burden of viral respiratory tract infections) affect AE events and that these effects differ among the different age groups. Thus strategies for prevention of AEs should be personalized and comprehensive, and multidisciplinary strategies to prevent AEs should be developed in response to changing outdoor environmental conditions.

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Clinical implications: Our findings provide evidence for the development of different strategies to prevent AE events in different age groups.

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TABLE E1. Detecting cross-map causal associations with multiple outdoor environmental factors

	Effects (cross-map skill [ρ_{CCM}])													
	Air pollutants					Weather condition			Aeroallergen			Viral respiratory tract infection		
Causes	PM_{10}	NO_2	O_3	CO	SO_2	Humidity	Solar sunshine	DTR	Tree	Grass	Weed	HRV	IFV	RSV
Air pollutants														
PM_{10}	NA	0.4837	0.1866	0.5101	0.5662	0.2135	0.0330	0.1112	0.0924	0.0331	0.1087	0.0000	0.1032	0.0225
NO_2	**0.5741***	NA	**0.3937**	**0.8031***	**0.6047***	**0.2874***	0.0005	**0.2469***	0.1117	0.0200	0.0722	0.0123	0.0718	0.0355
O_3	0.0390	**0.2360***	NA	**0.4086***	**0.2379***	0.0905	**0.2832***	**0.2630***	**0.4821***	**0.2451***	0.1416	0.0677	0.0378	0.3270
CO	**0.5646***	**0.7717***	0.5858	NA	**0.6533***	**0.2612***	0.0516	0.1324	0.1387	0.1172	0.1018	0.1016	0.0955	0.1419
SO_2	**0.6010***	**0.6052***	0.2986	**0.6771***	NA	**0.3404***	0.0715	0.1700	0.1880	0.1000	0.2293	0.0298	0.1100	0.1042
Weather condition														
Humidity	0.1668	0.1530	**0.2365***	0.1587	**0.2958***	NA	**0.6352***	**0.4594***	0.0447	0.0004	0.1466	0.0000	0.0873	0.0578
Solar sunshine	0.0520	0.0481	**0.2450***	0.0502	0.0945	**0.6111***	NA	**0.5302***	0.0038	0.0309	0.0117	0.0161	0.0051	0.0009
DTR	0.0967	0.1648	0.1973	0.1464	0.1340	**0.4440***	**0.6420***	NA	0.1096	0.1071	0.0097	0.0000	0.0138	0.0247
Aeroallergen														
Tree	0.0479	0.0491	0.1592	0.0554	0.0184	0.0506	0.0033	**0.2166***	NA	0.1142	0.1328	0.0000	0.0218	0.0130
Grass	0.0000	0.0433	0.1345	0.0286	0.0393	0.0062	0	0.0704	0.1681	NA	0.146	0.1078	0.0131	0.0485
Weed	0.0589	0.0822	0.0715	0.0767	0.0825	0.0397	0	0.0569	0.0218	**0.2056***	NA	0.0278	0.0993	0.0012
Viral respiratory tract infection														
HRV	0.0502	0.0555	0.0819	0.1017	0.1930	0.0499	0.0215	0.1146	0.0000	0.0394	0.1632	NA	**0.4419***	0.1262
IFV	0.1101	0.1094	0.0965	0.1316	0.2400	0.0567	0.0194	0.1276	0.0977	0.1505	0.1120	0.5340	NA	0.2171
RSV	0.0311	0.1492	0.4282	0.2270	0.0486	0.1542	0.1187	0.0202	**0.4392***	0.1982	0.1975	0.1051	0.0895	NA

NA, Not available.

*Numbers in boldface indicate statistically significant associations ($P < .05$) with high causal strength ($\rho_{CCM} > 0.2$).