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Original Article

Analysis of the Association Among Air Pollutants, Allergenic Pollen, and Respiratory Virus Infection of Children in Guri, Korea During Recent 5 Years

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ABSTRACT

Purpose: Concerns about the spread of infectious diseases have increased due to the coronavirus disease pandemic. Knowing the factors that exacerbate or increase the contagiousness of a virus could be a key to pandemic prevention. Therefore, we investigated whether the pandemic potential of infectious diseases correlates with the concentration of atmospheric substances. We also investigated whether environmental deterioration causes an increase in viral infections.
Methods: Pediatric patients (0–18 years old; n = 6,223) were recruited from those hospitalized for aggravated respiratory symptoms at Hanyang University Guri Hospital between January 1, 2015 and December 31, 2019. The number of viral infections was defined as the total number of virus-infected patients hospitalized for respiratory symptoms. We analyzed the association between the number of viral infections/week and the average concentrations of atmospheric substances including particulate matter (PM)10, PM2.5, O_3, NO_2, CO, SO_2, and allergenic pollen) for that week. The cross-correlation coefficient between the weekly measures of pollens and viral infections was checked to determine which time point had the most influence. The association of atmospheric substances in that time, with the number of viral infections/week was investigated using multiple linear regression analysis to identify factors with the greatest influence.
Results: In spring the tree pollen average concentration one week earlier (t-1) had the greatest correlation with the average virus infection of a given week (t) ($\rho XY(h)$ =0.5210). The number of viral infections showed a statistically significant correlation with especially tree pollen concentration of 1 week prior (adj R^2=0.2280). O_3 concentration was correlated to the number of viral infections within that week (adj R^2=0.2552) in spring, and weed pollen and CO concentration correlated (adj R^2=0.1327) in autumn.
Conclusions: Seasonal co-exposure to air pollutants and allergenic pollens may enhance respiratory viral infection susceptibility in children. Therefore, reducing the concentrations of air pollutants and pollens may help prevent future epidemics.

Keywords: Respiratory viral infection; respiratory symptom, air pollutant; pollen; children

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INTRODUCTION

Acute respiratory viral infections are the most common ones among children, accounting for 30%–50% of all outpatient visits and resulting in the deaths of millions of children annually worldwide.[1,2] For children in high-risk groups, including those aged < 3 years, low birth weight infants, or those attending daycare, as respiratory viral infections progress, hospitalization is often required to lower the risk of respiratory tract diseases, such as pneumonia and bronchiolitis.[3,4]

Typically, respiratory viruses are highly contagious because of the nature of infection, and it is critical to understand the patterns of an epidemic as many people can be infected in a short period.[5] In recent years, concerns about the spread of infectious diseases have increased due to the H5N1 avian influenza, severe acute respiratory syndrome (SARS), and coronavirus disease 2019 (COVID-19) pandemics, and countermeasures are being taken around the world.[6,7]

The World Health Organization defines air pollution as contamination of the indoor or outdoor environment by any chemical, physical, or biological agent that modifies the natural characteristics of the atmosphere. These agents directly affect human health; thus, they are environmental problems.[8,9] Metropolitan areas have high population densities as well as high levels of transportation and industrial activity that deteriorate the atmospheric environment.[10,11] In addition, most residences and schools are located near roads, which can often present a threat of exposure to air pollutants, such as particulate matter (PM), ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). Air pollution is gaining attention as it continues to adversely affect human health. CO, SO_2, and NO_2, which are representative substances, are generated from the combustion of fossil fuels and can cause lung and respiratory diseases.[10-12] Interest in PM has also been growing recently. PM affects asthmatic patients by increasing their hospitalization rate, worsening respiratory symptoms, and hindering lung function.[9,13,14]

Pollen is a seasonal aeroallergen that causes allergies.[15,16] There are 2 peak pollen seasons in Korea; tree pollen is common in spring, while the amount of weed pollen is high in autumn.[17,18] There is an overwhelming consensus that ongoing increases in CO_2 and other anthropogenic infrared-absorbing gases are and will continue to alter several climatic variables. If, as expected, the impact of climate change continues to intensify, there is a critical need to assess the impact of these factors on aeroallergens, allergic diseases, and overall respiratory health.[19-21] Pollen worsens respiratory symptoms in people who are sensitive to it and can even worsen symptoms in patients with no sensitivity to pollen.[15,16,22] However, there are few studies on whether pollen exacerbates both respiratory symptoms and viral infections in people who are not sensitized to it. Pollution and exposure to respiratory viruses, particularly rhinovirus, can worsen respiratory symptoms and exacerbate asthma.[23] Airborne pollen constitutes a significant fraction of bioaerosols and serves as a viral carrier.[24]

Therefore, we investigated whether the pandemic potential of respiratory infectious diseases correlates with current environmental pollutant and allergenic pollen concentrations, and whether the deterioration of the environment increases the burden of viral infections. In this study, we focused on multiple pollutants, such as PM10, PM2.5, O_3, NO_2, CO, SO_2, and allergenic pollen, all of which are known to have a significant impact on humans,[10,12] and we examined their association with respiratory viral infections. The purpose of this study was to

determine whether the concentrations of air pollutants and pollens affect the prevalence of respiratory viral infections.

MATERIALS AND METHODS

Ethical considerations

This study was approved by the Institutional Review Board (IRB) of Hanyang University Guri Hospital, Gyeonggi-Do, South Korea (IRB No. 2021-07-044-001). The requirement for written informed consent was waived because of its retrospective study design. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Participant recruitment

The concentration of air pollutants varies greatly across regions. Therefore, we limited our study to a suburban area of Seoul (Guri and Namyangju, Gyeonggi-Do, South Korea), which ensures good access to the Hanyang University Guri Hospital by nearby residents.

To analyze the associations between the number of viral infections and atmospheric substances to which patients were actually exposed, only patients with no significant difference between their residence and their main living radius were included in the study.

As most adults spend a considerable amount of their time working, there is a difference between their living and working areas. Thus, the actual concentrations of atmospheric substances and pollens in the patient's residence differ from the patient’s actual exposure. However, these environments are almost identical for children. Therefore, we recruited only patients aged < 18 years who were living in the designated study areas. Children aged 0 to 18 years who were hospitalized for respiratory symptoms, such as dyspnea, cough, sputum, and fever at the Hanyang University Guri Hospital from January 1, 2015 to December 31, 2019, were recruited for this study. Among these patients, those with confirmed respiratory viral infections were selected as the final participants.

Viral testing

Viral infection testing was performed for the hospitalized patients with respiratory symptoms on the day of hospitalization using the nasal swab method. Testing was performed for 12 viruses, including adenovirus, influenza A and B viruses, human metapneumovirus, human coronavirus, parainfluenza virus, respiratory syncytial virus (RSV) types A and B, human rhinovirus, and human bocavirus. All viruses were detected using a multiplex real-time polymerase chain reaction assay (Allplex TM Respiratory Panel 1, 2, 3, Seegene, Seoul, Korea). The patients were determined to have an infection if they yielded positive results for at least one of the subtypes tested.

Air pollutants

The PM and air pollutant concentrations were measured in Namyangju and Guri. The daily and weekly average concentration data for PM10, PM2.5, O_3, NO_2, CO, and SO_2 were collected from January 1, 2015 to December 31, 2019 using data published by the Ministry of Environment (www.airkorea.or.kr).

Pollen

Pollen was collected at Hanyang University Guri Hospital from January 1, 2015 to December 31, 2019. The distribution of pollen was measured daily by installing a 7-day recording volumetric spore trap (Burkard Manufacturing Co., Hertfordshire, UK) at a height of 1.5 m from the surface of the hospital roof. We collected weekly drums that collected pollens from the air and had them examined by 2 specialists. The glycerin-adhesive vinyl was stained with Calberla's fuchsin solution (10 mL glycerin, 20 mL 95% alcohol, 30 mL distilled water, and 0.2 mL basic fuchsin) and identified under a 400-fold magnification optical microscope (OLYMPUS/BX43). The number of pollen grains/species/m^3 was calculated and recorded. The pollens were categorized according to size, shape, and surface pattern depending on the allergy-related plants distributed in each region.

Statistical analysis

Statistical analysis was performed by dividing the observed atmospheric substance concentrations by the seasonal distribution of respiratory viral infections and air pollutants during the 5-year study period (2015–2019).

Many factors, including temperature and humidity, can influence respiratory viral infections. To reduce the effect of variations in atmospheric environmental variables, we performed our analysis within a period of similar environmental variables. Therefore, the correlations between air pollution, pollen concentration, and the number of viral infections were analyzed by dividing into 2 periods (spring and autumn).

The correlation between respiratory viral infections and the concentration of air pollutants was analyzed for the spring season, which was defined as February to June. Tree pollen was primarily observed during this period. During the spring, the atmospheric substance concentrations were measured as the concentrations of air pollutants and tree pollens. Weed pollen was primarily observed during the period from August to November, which was defined as the autumn season. In this season, atmospheric substance concentrations were measured as the concentrations of the air pollutants and weed pollens. We analyzed the association between the weekly number of infections and the average concentration of air pollutants and pollens for that week. First, the cross-correlation coefficient between the weekly measures of pollens and viral infections was checked to determine which time point had the most influence. Then, the association of pollen concentration and air pollutants (PM10, PM2.5, O_3, NO_2, CO, and SO_2) in that time, with the number of viral infections/week was investigated using multiple linear regression analysis to identify factors with the greatest influence.

RESULTS

Demographic information

Over the 5-year study period, 6,223 patients under 18 years of age were hospitalized for respiratory symptoms. The mean age of the patients was 3.74 ± 3.61 years; there were 3,476 boys and 2,748 girls. Confirmed respiratory viruses were detected in 4,058 of the patients (mean age, 2.96 ± 2.91 years), of whom 2,265 were boys and 1,793 were girls.

Detected virus types

The distribution of the respiratory viruses identified among patients hospitalized during the 5-year period are as follows: rhinovirus (1,295 cases), adenovirus (983), RSV (656),

bocavirus (452), parainfluenza (439), influenza (389), human metapneumovirus (246), and coronavirus (240).

Spring (tree pollen season)

In spring, when the cross-correlation coefficient was analyzed, the tree pollen average concentration one week earlier (t-1) had the greatest correlation with the average virus infection of a given week (t) ($\rho XY(h)$ =0.5210, **Table 1**). Therefore, we analyzed whether the pollen and air pollutant concentrations one week earlier (t-1) affected the number of viral infections. The association between the number of viral infections (t)/week and the average concentrations of the atmospheric substances (t-1)/week were analyzed using multiple linear regression. The number of viral infections showed no statistically significant correlation with the concentrations of the air pollutants one week earlier (t-1); however, it did show a statistically significant correlation with the tree pollen concentration one week earlier (t-1) (adj R^2 = 0.2280, **Table 2**). Even when atopic children with a pollen allergy and the non-atopic group of children were analyzed separately, there was a significant correlation between the respiratory virus infection rate and the tree pollen concentration for both groups, regardless of the presence of allergies (**Figure**).

When analyzed at time (t), there was a statistically significant correlation with O_3 rather than pollen (adj R^2 = 0.2552, **Table 3**).

Autumn (weed pollen season)

In autumn, when the cross-correlation coefficient was analyzed, the tree pollen average concentration of that week (t) had the strongest correlation on the average virus infection (t) ($\rho XY(h)$ = 0.154, **Table 1**). Therefore, we analyzed whether the pollen and air pollutant concentrations at that week (t) affected viral infections.

The association between the number of viral infections(t)/week and the average concentrations of the atmospheric substances(t)/week were analyzed using multiple linear regression, which showed a statistically significant correlation with the weed pollen and CO concentrations (adj R^2 = 0.1327, **Table 4**).

Table 1. Cross-correlation coefficients between the number of infections (t) and pollen concentration (t-n)

Variables	t-5	t-4	t-3	t-2	t-1	t
In spring $\rho XY(h)$	0.1171	0.2137	0.301	0.4593	**0.5210**	0.4512
In autumn $\rho XY(h)$	0.026	0.028	0.055	0.068	0.016	**0.154**

The pollen concentration was highest 1 week before the highest viral infection. Bold indicate highest cross-correlation coefficient.
t-n, n weeks ago; $\rho XY(h)$, cross-correlation coefficient.

Table 2. A multiple linear regression analysis of the number of infections (t-1)/week (*y*) and the concentration of tree pollen (t-1) + air pollution (t-1) /week (*x*) in the spring

Variables	Estimate (b_i)	Standard error	*P* value
Tree pollen	**0.0089**	**0.002001**	**< 0.001**
PM10	−0.0143	0.054038	0.7914
PM2.5	−0.1070	0.123217	0.3874
O_3	222.4119	109.235583	0.0444
NO_2	−89.0216	163.664777	0.5877
CO	3.6179	11.277106	0.749
SO_2	688.1015	879.551986	0.4359

The number of infection (t) = $b0$ + $b1$ × tree pollen (t-1) + $b2$ × PM10 (t-1) + $b3$ × PM2.5 (t-1) + $b4$ × O_3 (t-1) + $b5$ × NO_2 (t-1) + $b6$ × CO (t-1) + $b7$ × SO_2 (t-1).
Bold indicate statistically significant.
PM10, particulate matter 10; PM2.5, particulate matter 2.5; O_3, ozone; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide.

Figure. The correlation between the concentration of tree pollens and the number of respiratory viral infections during the spring over a 5-year period, from 2015 to 2019. Pollen increased the number of respiratory viral infections within 1 week, regardless of the allergy status of the children in the study. (A) Viral infections in atopic children. (B) Viral infections in non-atopic children. The red line expresses the number of detected viruses, and the blue line expresses the amount of tree pollen.

Table 3. A multiple linear regression analysis of the number of infections (t)/week (*y*) and the concentration of tree pollen (t) + air pollution (t) /week (*x*) in the spring

Variables	Estimate (b_i)	Standard error	Pr (>|t|)
Tree pollen	0.008	0.0062	0.1648
PM10	0.0252	0.03929	0.5236
PM2.5	−0.1426	0.07836	0.0726
O_3	225.92	74.50	**0.0032**
NO_2	88.14	103.6	0.3973
CO	−9.2306	8.009	0.2526
SO_2	1,093	663.0	0.1033

The number of infection (t) = *b0* + *b1* × tree pollen (t) + *b2* × PM10 (t) + *b3* × PM2.5 (t) + *b4* × O_3 (t) + *b5* × NO_2 (t) + *b6* × CO (t) + *b7* × SO_2 (t).
Bold indicate statistically significant.
PM10, particulate matter 10; PM2.5, particulate matter 2.5; O_3, ozone; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide.

Table 4. A multiple linear regression analysis of the number of infections (t) /week (*y*) and the concentration of weed pollen (t) + air pollution (t)/week (*x*) in the autumn

Variables	Estimate (b_i)	Standard error	Pr (>|t|)
Weed pollen	0.0426	0.0170	**0.0153**
PM10	−0.0031	0.1078	0.9773
PM2.5	−0.0822	0.1809	0.6514
O_3	86.8608	110.4127	0.4347
NO_2	32.0053	129.5292	0.8057
CO	13.8352	5.9359	**0.0233**
SO_2	27.5962	591.9069	0.9630

The number of infections (t) = *b0* + *b1* × tree pollen (t) + *b2* × PM10 (t) + *b3* × PM2.5 (t) + *b4* × O_3 (t) + *b5* × NO_2 (t) + *b6* × CO (t) + *b7* × SO_2 (t).
Bold indicate statistically significant.
PM10, particulate matter 10; PM2.5, particulate matter 2.5; O_3, ozone; NO_2, nitrogen dioxide; CO, carbon monoxide; SO_2, sulfur dioxide.

DISCUSSION

Some of the atmospheric substances in this study were associated with the number of viral infections in the 2 seasons. These associations varied both in strength and by season. In spring, the number of virus-infected patients had a high correlation with the tree pollen concentration one week earlier. At that time (t-1), other air pollutants had no significant correlation with the number of viral infections. However, when the correlation between virus infections and atmospheric material concentrations at time (t) was investigated, the concentration of O_3 showed a correlation. In autumn, the number of virus-infections was correlated with the weed pollen concentrations of that week. So, when the correlation between atmospheric substances and the number of virus infections was investigated at the time (t), the number of viral infections was associated with the concentrations of some atmospheric substances, particularly tree pollens and CO.

Several studies have shown an association between the concentration of atmospheric substances and the degree to which respiratory symptoms worsened. Pollen exposure weakens the body's innate defense against respiratory viruses.[25] According to a recent report of 31 countries, higher airborne pollen concentrations correlate with increased SARS coronavirus-2 infection rates.[26] In addition, Brauer *et al.*[10] have reported that children who live close to major roads and are exposed to air pollution have an elevated risk of asthma and respiratory diseases. Ierodiakonou *et al.*[27] have reported that in areas with high concentrations of air pollution, children experienced reduced lung function and developed bronchial hypersensitivity. Other studies have shown that air pollution from traffic can lead to the development of respiratory infections and asthma and allergic symptoms in children.[12]

It is difficult to determine the actual level of atmospheric substances a person is exposed to at any given time. Therefore, to compensate for this limitation, we designated a specific area as the area of interest for our study and only recruited pediatric patients who were living in that area, as their residences and primary living spaces would be nearly identical. The concentrations of various atmospheric substances in that area were also measured. The results of this study showed that a high concentration of atmospheric substances-especially tree pollen concentration of 1 week earlier, O_3 concentration of that week in spring, and weed pollen and CO concentration of that weeks in autumn raised the levels of viral infection. These results show that some atmospheric substances can not only worsen respiratory symptoms but can also increase viral infections.

There are several possible reasons for these seasonal differences. The factors associated with viral infections are different for each virus epidemic season. First, viruses like the human rhinovirus are more prevalent during spring, while RSV and coronavirus are more common in autumn. Consequently, the observed seasonal differences may be due to different factors affecting each virus. This may be due to differences in seasonal and other environmental factors such as temperature and humidity. Also, the absolute concentration of atmospheric substances varies by season. This may be why the substances affecting viral s vary by season.

Exposure to pollution can worsen respiratory symptoms and exacerbate asthma.[23] The respiratory effect of atmospheric substances primarily occurs via an inflammatory response that includes the secretion of cytokines and chemokines, an increase in the number of white blood cells, and production of reactive oxygen species in the bronchioles. This inflammatory response can cause or worsen asthma, chronic bronchitis, and airway obstruction as well as the response

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of cells and tissues to endotoxins. It also increases free radical levels and oxidative stress.[28] This may explain why an increase in the concentration of air pollutants led to an increase in the rate of respiratory viral infections in this study. Previous studies have demonstrated that ambient air pollution is associated with a person's susceptibility to respiratory viral infections. Exposure to air pollutants can cause neutrophil infiltration, monocyte differentiation, and an increase in Th17 cells, which may contribute to the severity of viral infections and subsequent respiratory diseases.[29] Exposure to ozone increases sputum production and modifies the cell surface phenotypes of antigen-presenting cells in healthy subjects. Additionally, lung function is reduced and neutrophilic airway inflammation is increased in healthy subjects following exposure to ozone.[30,31] The angiotensin-converting enzyme 2 (ACE-2) receptor that is involved in the coronavirus colonization of the respiratory epithelial cells is over-expressed during chronic exposure to air pollutants. Air pollution also damages the respiratory tract and increases the activity of ACE-2, which, in turn, enhances the uptake of the virus.[32,33] Determining whether airborne pollen acts as a potent carrier for respiratory virus transport, dispersal, and proliferation requires additional multidisciplinary research. Furthermore, additional research is needed to show how pollen bioaerosols affect virus survival and community spread.[34]

This study has some limitations. First, as a single-center study, there were regional and time limitations that resulted in a limited number of cases, as only patients with severe disease who required hospitalization were included. Patients requiring outpatient treatment for low-severity illnesses were excluded. Therefore, the number of infected patients was lower than the hospitalized patients, which resulted in a small number of study participants (n = 6,223). In addition, the number of infected patients was too small to analyze each respiratory virus according to epidemic period. Thus, we attempted to investigate the effect of atmospheric substances on the respiratory viral infection regardless of the virus type. As individual viruses have unique characteristics, their infections may also differ. A large-scale study involving multiple centers with a broader time and patient scope will be required in the future. Secondly, the indoor air pollutant concentration to which patients were exposed could not be calculated. Many previous studies have shown that indoor air quality is worse than outdoor air quality. However, indoor air quality has improved with advances in ventilation systems.[35,36] Therefore, it would also be useful to define the air pollutant concentration in the atmosphere as the air pollutant concentration the patient is actually exposed to. Thirdly, we analyzed the association between the virus detection rate on the day of hospitalization and the concentration of air pollutants on the same day. Since viruses have an incubation period after infection, the day a virus is detected is not the same as the date of infection. To compensate for this, we analyzed the average concentrations of the atmospheric substances for a week and the total number of patients and viral infections that occurred in that same week. Finally, there were more environmental variables that interacted with each other than just those analyzed in this study. To reduce the effect of differences in atmospheric environmental variables, we tried as much as possible to perform our analysis within a period of similar environmental variables. Therefore, the correlations between air pollution, pollen concentration, and virus infection were analyzed by separating the spring and autumn seasons.

Despite these limitations, it is very meaningful that the present study evaluated the correlation between viral infection and air pollution as well as allergic pollen concentration.

In recent years, respiratory viral infections, such as influenza, SARS, and especially COVID-19, have spread rapidly throughout communities and caused serious social and economic losses. Therefore, prevention of these infections is critical. Based on the findings

of this study, reduction in the concentration of air pollutants is expected to play a significant role in the prevention of viral infections.

In conclusion, the results of this study show that atmospheric substances, especially tree pollen concentration of 1 week prior, O_3 concentration of that week in spring, and weed pollen and CO concentration of that weeks in autumn, raised the respiratory viral infections in Korean children. Based on these findings, we believe that reduction in the concentration of pollutants can be a preventive measure against future epidemics. Therefore, further large-scale, well-characterized cohort studies are needed to demonstrate a more accurate association between atmospheric substances and viral infection.

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