



The Effects of Short-Term and Very Short-Term Particulate Matter Exposure on Asthma-Related Hospital Visits: National Health Insurance Data

Dae Jin Song^{1,2}, Sun Hee Choi³, Woo-Jung Song⁴, Kyung Hee Park⁵, Young-Koo Jee⁶, Sang-Heon Cho^{7,8}, and Dae Hyun Lim^{9,10}

¹Department of Pediatrics, Korea University College of Medicine, Seoul;

²Environmental Health Center for Asthma, Korea University Anam Hospital, Seoul;

³Department of Pediatrics, School of Medicine, Kyung Hee University, Seoul;

⁴Department of Allergy and Clinical Immunology, Asan Medical Center, University of Ulsan College of Medicine, Seoul;

⁵Department of Internal Medicine, Institute of Allergy, Yonsei University College of Medicine, Seoul;

⁶Department of Internal Medicine, Dankook University College of Medicine, Cheonan;

⁷Department of Internal Medicine, Seoul National University College of Medicine, Seoul;

⁸Institute of Allergy and Clinical Immunology, Medical Research Center, Seoul National University, Seoul;

⁹Department of Pediatrics, Inha University College of Medicine, Incheon;

¹⁰Environmental Health Center for Allergic Diseases, Inha University Hospital, Incheon, Korea.

Purpose: The purpose of this study was to investigate the effects of short-term and very short-term exposure to particulate matter (PM) exceeding the daily average environmental standards for Korea ($\leq 100 \ \mu g/m^3$ for PM₁₀ and $\leq 50 \ \mu g/m^3$ for PM_{2.5}) on on asthma-related hospital visits.

Materials and Methods: This was a population-based, case-crossover study using National Health Insurance and air pollution data between January 1, 2014 and December 31, 2016. The event day was defined as a day when PM exceeded the daily average environmental standard (short-term exposure) or daily average environmental standard for 2 hours (very short-term exposure). The control day was defined as the same day of the week at 1 week prior to the event day.

Results: Compared with control days, asthma-related hospital visits on the 24-hr event days and 2-hr event days increased by 4.10% and 3.45% for PM_{10} and 5.66% and 3.74% for $PM_{2.5}$, respectively. Asthma-related hospital visits increased from the 24-hr event day for PM_{10} to 4 days after the event day, peaking on the third day after the event day (1.26, 95% confidence interval, 1.22–1.30). Hospitalizations also increased on the third day after the event. While there was a difference in magnitude, $PM_{2.5}$ exposure showed similar trends to PM_{10} exposure.

Conclusion: We found a significant association between short-term and very short-term PM exposure exceeding the current daily average environmental standards of Korea and asthma-related hospital visits. These results are expected to aid in establishing appropriate environmental standards and relevant policies for PM.

Key Words: Particulate matter, asthma, outpatients, National Health Insurance

Received: May 10, 2019 Revised: August 13, 2019 Accepted: August 14, 2019

Co-corresponding authors: Dae Hyun Lim, MD, PhD, Department of Pediatrics, Inha University College of Medicine, 27 Inhang-ro, Joong-gu, Incheon 22332, Korea. Tel: 82-32-890-3658, Fax: 82-32-890-2629, E-mail: dhyunlim@inha.ac.kr and

Sang-Heon Cho, MD, PhD, Department of Internal Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea. Tel: 82-2-760-2971, Fax: 82-2-764-3954, E-mail: shcho@plaza.snu.ac.kr

•The authors have no potential conflicts of interest to disclose.

© Copyright: Yonsei University College of Medicine 2019

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

The impact of air pollution on health has been a global issue for decades.¹ However, it remains an emerging problem in several regions, including Asia. Particulate matter (PM), which is a common measure of air pollution, is a complex mixture of solid and liquid particles suspended in the atmosphere. It is categorized by its aerodynamic diameter, such as PM_{10} ($\leq 10 \ \mu m$) and $PM_{2.5}$ ($\leq 2.5 \ \mu m$). The former is mainly produced by construction activities and re-suspension of road dust and wind, while the latter arises mainly from combustion processes. The composition of PM may vary depending on the area where PM is generated, the season, and weather conditions.² According to recent statistics from the World Health Organization, the mean annual concentration of PM_{2.5} is still very high and even continues to increase in Asian countries, like China, India, and Korea.³

The range of health effects of PM is broad, but are predominantly to the cardiovascular and respiratory systems.⁴ All populations can be affected, but patients with chronic respiratory disease, such as asthma, are considered to be more vulnerable to the harmful health effects of PM. Many epidemiologic studies have shown the association between air pollution and risks of asthma exacerbations and hospitalizations.⁵⁻⁹ The effects of PM may vary with local environment (environmental standards for PM, the compositions of PM, and medical systems) or population characteristics. Therefore, the health impact assessment performed in each country has its own significance. In addition, to our knowledge, few studies have investigated the effects of PM on overall asthma-related hospital visits, including outpatient visits. The majority of available studies have measured asthma-related emergency room visits or hospitalization only, which is a marker for severe asthma exacerbations: the severe outcomes reflect only a small portion of asthma deterioration, and the number of outpatient visits may better reflect changes in asthma activities, including mild asthma attacks. Furthermore, the effects of short-term exposure so far have only been assessed using daily average concentrations of PM, and few have examined the effects of shorter exposure (e.g., 1 or 2-hours). Interestingly, a recent study suggested the possibility that hourly increases in air pollution may increase the risk of asthma exacerbation.10

Because the medical system of Korea is based on the National Health Insurance (NHI) system, the NHI database includes data on all nationwide outpatient visits, emergency room visits, and hospital admissions, providing an opportunity to examine the association between PM exposure and asthma-related hospital visits as a whole. Korea has been monitoring and managing PM_{10} and $PM_{2.5}$ from 2001 and 2015, respectively. However, the number of days exceeding the daily average environmental standard has been increasing in recent years, especially in the winter and spring seasons. Previous studies have defined asthma-related hospital visits based on only the International Classification of Diseases, 10th revision codes (ICD-10 codes) for The purpose of this study was to investigate the effects of short-term exposure to PM exceeding the daily average environmental standards of Korea on asthma exacerbations based on recent NHI data with a more reliable definition of asthmarelated hospital visits. We also investigated the effects of very short-term PM exposures (PM exposure exceeding the daily average environmental standards for 2 hours) on asthma-related hospital visits.

MATERIALS AND METHODS

Study subjects and design

This was a population-based, case-crossover study designed to investigate the effect of short-term exposure to PM exceeding the environmental standards of Korea on asthma exacerbations using the NHI data between January 1, 2014 and December 31, 2016. The daily average environmental standards of Korea are $\leq 100 \,\mu\text{g/m}^3$ for PM₁₀ and $\leq 50 \,\mu\text{g/m}^3$ for PM_{2.5}. The event day was defined as a day when PM exceeded the daily average environmental standard (24-hr event day) or as a day when PM exceeded the daily average environmental standard for 2 hours (2-hr event day). The control day was defined as the same day of the week, 1 week prior to the event day. The first day was selected if an event lasted for more than 1 day. Among the dates selected as the event days, the following cases were excluded: 1) all holidays and weekends on which outpatient clinics were closed; 2) another PM event within 14 days prior to the event day, which could affect the control day; 3) a precipitation difference of more than 10 mm and a statistical difference in temperature and humidity between the event day and control day.

Changes in the number of asthma-related hospital visits per day were observed for 5 days after the event day. Asthma-related hospital visits were defined according to following criteria: 1) ICD-10 codes J45.x–J46.x for the principal or additional diagnoses; 2) prescription of one asthma medication, such as inhaled corticosteroids (ICSs), long acting b2-agonists (LABAs), ICS and LABA combined in a single inhaler (ICSs/LABAs), oral leukotriene antagonists, short-acting b2-agonists, long-acting muscarinic antagonists, systemic corticosteroids, and theophylline derivatives; 3) in case of emergency room visits and hospitalization, prescription of one asthma rescue medication, such as systemic steroids (oral or iv), short-acting beta 2-agonist, or theophylline derivatives.

Data source and ethics

We used NHI claims data provided by the Korean NHI Service, as well as climate data provided by the Korea Meteorological Administration. Air pollution data over the same period (i.e., between January 1, 2014 and December 31, 2016) were obtained from the National Institution of Environmental Research, which

YМJ

included PM₁₀ and PM_{2.5} levels for metropolitan areas (Seoul, Incheon, and Gyeonggi), Busan, Daegu, Daejeon, and Jeju Island. For PM_{2.5}, the environmental standard was established as the "interim target-II" (25 μ g/m³ annual average, 50 μ g/m³ daily average) in WHO guidelines in 2011, and application of the standard was began in 2015. Therefore, in order to evaluate the impact of PM_{2.5}, we used the data from Seoul and Busan in 2015 and 2016, as these cities have a relatively large number of monitoring stations. This study was approved by the Institutional Review Board of Inha University Hospital (approval No. INHAUH 2017-05-005).

Statistical analysis

The Wilcoxon signed rank test was used to determine differences in climate between the event day and the control day. The chi-square test and Fisher's exact test were used to evaluate changes in asthma-related hospital visits on the event days, compared to the control days. A log Poisson regression model was also used to compare relative risks. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and p values<0.05 were considered statistically significant.

RESULTS

Selection of event days

The numbers of 24-hr event days that met the eligibility criteria for PM_{10} and $PM_{2.5}$ were 26 days and 12 days, respectively. The total numbers of 2-hr event days that met the eligibility criteria for PM_{10} and $PM_{2.5}$ were 31 days and 12 days, respectively. There were no significant differences in meteorological data between the event days and the control days (Supplementary Tables 1–5, online only).

Effects of exposure to PM₁₀ exceeding the daily average environmental standard on asthma-related hospital visits

The average number of asthma-related hospital visits per day on the 24-hr event days and 2-hr event days for PM_{10} were increased by 4.10%, and 3.45% compared with the control days, respectively (Table 1). Outpatient visits increased, whereas emergency room visits and hospitalizations did not increase on both the 24-hr event days and 2-hr event days. Asthma-related hospital visits increased regardless of sex and were significantly greater in patients over 65 years and in those 13–18 years of age when compared with other age groups for the 24-hr event days and 2-hr event days. Hospital visits due to asthma increased in the health insurance group, but not in the medical aid group on both the 24-hr event days and 2-hr event days.

$Effects \ of \ exposure \ to \ PM_{2.5} \ exceeding \ the \ daily \\ average \ environmental \ standard \ on \ asthma-related \\ hospital \ visits$

The average number of asthma-related hospital visits per day on the 24-hr event days and 2-hr event days for $PM_{2.5}$ increased by 5.66% and 3.74%, compared with the control days, respectively (Table 2). Only outpatient visits increased on the 24-hr event days, whereas outpatient visits and emergency room visits increased on 2-hr event days. Increases were significant regardless of sex and in patients under 12 years and over 65 years

Table 1. Comparison of Asthma-Related Hospital Visits between Control and Event Days for PM₁₀

	24-hr event day						2-hr event day					
	Control day		Event day		%		Control day		Event day		%	nualua
	n	%	n	%	change	<i>p</i> value	n	%	n	%	change	<i>p</i> value
Total	44301	49.00	46116	51.00	4.10	< 0.001	25430	49.15	26307	50.85	3.45	<0.001
Sex						0.282						0.549
Male	21008	49.19	21704	50.81	3.31	< 0.001	11740	49.01	12214	50.99	4.04	<0.001
Female	23293	48.83	24412	51.17	4.80	< 0.001	13690	49.27	14093	50.73	2.94	< 0.001
Age (yr)						0.019						0.037
≤12	23693	49.45	24219	50.55	2.22	< 0.001	11439	49.07	11871	50.93	3.78	< 0.001
13–18	859	47.20	961	52.80	11.87	< 0.001	469	46.81	533	53.19	13.65	0.005
19–55	8053	48.96	8396	51.04	4.26	< 0.001	4991	49.87	5017	50.13	0.52	0.724
56–65	4003	48.46	4258	51.54	6.37	< 0.001	2929	50.26	2899	49.74	-1.02	0.591
>65	7693	48.16	8282	51.84	7.66	< 0.001	5602	48.34	5987	51.66	6.87	<0.001
Asthma-related hospital visits						0.867						0.051
Hospitalization	1470	49.48	1501	50.52	2.11	0.436	1092	51.51	1028	48.49	-5.86	0.053
Emergency room	273	49.01	284	50.99	4.03	0.549	157	51.99	145	48.01	-7.64	0.371
Outpatient	42558	48.98	44331	51.02	4.17	<0.001	24181	49.03	25134	50.97	3.94	<0.001
Insurance type						0.728						0.835
Health insurance	42296	48.98	44051	51.02	4.15	<0.001	23853	49.16	24664	50.84	3.40	< 0.001
Medical aid	2005	49.26	2065	50.74	2.99	0.191	1577	48.98	1643	51.02	4.19	0.105

of age on the 24-hr event days, compared with other age groups. On 2-hr event days, asthma-related hospital visits were significantly increased in males and in patients under 12 years old. Hospital visits due to asthma increased in the health insurance group, but not in the medical aid group on both the 24-hr event days and 2-hr event days.

Changes in asthma-related hospital visits due to PM exposure over time

To compare the relative risks over time, a log Poisson regression analysis was conducted, in which climate, age, sex, income, type of medical insurance, and region were controlled for. For PM_{10} , the ratio of an average number of asthma-related hospital visits per day increased starting on the 24-hr event day [ratio, 1.0857, 95% confidence interval (CI) 1.0502–1.1225] until 4 days after the event day, peaking on the third day after the event day (ratio, 1.2633, 95% CI, 1.2234–1.3046) (Table 3). Hospitalizations also increased on the third day after an event (Table 4). For $PM_{2.5}$, although there was a difference in magnitude, the observed trends were similar to those for PM_{10} exposure (Tables 3 and 4).

Table 2. Comparison of Asthma-	Related Hospital Visits between	Control and Event Days for PM _{2.5}

	24-hr event day						2-hr event day					
	Control day		Event day		%		Contro	ol day	Even	t day	%	
	n	%	n	%	change	<i>p</i> value	n	%	n	%	change ¹	<i>p</i> value
Total	13014	48.62	13751	51.38	5.66	<0.001	11357	49.08	11782	50.92	3.74	<0.001
Sex						0.966						0.011
Male	5958	48.61	6299	51.39	5.72	<0.001	5140	48.18	5529	51.82	7.57	< 0.001
Female	7056	48.64	7452	51.36	5.61	< 0.001	6217	49.86	6253	50.14	0.58	0.658
Age (yr)						0.050						0.007
≤12	5957	47.80	6505	52.20	9.20	< 0.001	4745	47.79	5184	52.21	9.25	<0.001
13–18	211	47.20	236	52.80	11.85	0.108	220	49.44	225	50.56	2.27	0.789
19–55	2488	49.38	2550	50.62	2.49	0.224	2325	50.05	2320	49.95	-0.22	0.934
56-65	1536	50.54	1503	49.46	-2.15	0.412	1433	51.31	1360	48.69	-5.09	0.054
>65	2822	48.83	2957	51.17	4.78	0.013	2634	49.45	2693	50.55	2.24	0.261
Asthma-related hospital visits						0.349						0.154
Hospitalization	482	50.47	473	49.53	-1.87	0.714	470	48.11	507	51.89	7.87	0.103
Emergency room	54	44.63	67	55.37	24.07	0.123	53	41.09	76	58.91	43.40	0.006
Outpatient	12478	48.57	13211	51.43	5.87	<0.001	10834	49.17	11199	50.83	3.37	0.001
Insurance type						0.060						0.540
Health insurance	12220	48.48	12986	51.52	6.27	< 0.001	10603	49.14	10976	50.86	3.52	< 0.001
Medical aid	794	50.93	765	49.07	-3.65	0.316	754	48.33	806	51.67	6.90	0.068

Table 3. The Ratio of the Average Number of Asthma-Related Hospital Visits per Day on Event and Control Days

		Event day	Day +1	Day +2	Day +3	Day +4	Day +5
PM ₁₀	exp(β)*	1.0857	1.1519	1.1212	1.2633	1.1252	0.2547
	95% CI	1.0502-1.1225	1.1147-1.1904	1.0847-1.1588	1.2234-1.3046	1.0886-1.1629	0.2415-0.2687
PM _{2.5}	exp(β)	1.0684	1.0097	1.0043	1.071	0.9866	0.3803
	95% CI	1.0017-1.1395	0.9458-1.0779	0.9407-1.0723	1.0041-1.1423	0.9239-1.0537	0.3482-0.4154

CI, confidence interval.

*exp(β)- ratio of the average number of asthma-related hospital visits per day: average number of asthma-related hospital visits on the event days/average number of asthma-related hospital visits on the control days.

Table 4. The Ratio of the Average Number of Asthm	a-Related Hospitalization per Day on Event and Control Days

		5		, ,		1	
		Event day	Day +1	Day +2	Day +3	Day +4	Day +5
PM ₁₀	exp(β)*	1.0114	1.1833	0.9228	1.4937	0.8374	0.6908
	95% CI	0.8439-1.2122	0.9939-1.4087	0.7667-1.1107	1.2654-1.7633	0.6924-1.0128	0.5651-0.8445
PM _{2.5}	exp(β)	1.0507	0.8909	0.7376	1.3725	0.8711	0.6104
	95% CI	0.7579-1.4567	0.6337-1.2526	0.5152-1.0561	1.0093-1.8666	0.6183-1.2271	0.4175-0.8924

CI, confidence interval.

*exp(β)- ratio of the average number of asthma-related hospitalization per day: average number of asthma-related hospitalization on the event days/average number of asthma-related hospitalization on the control days.

DISCUSSION

In this study, we found that the average number of asthma-related hospital visits increased on the day exceeding the daily average environmental standard for PM ($PM_{10} \ge 100 \ \mu g/m^3$ or $PM_{2.5} \ge 50 \ \mu g/m^3$). This increase was observed even on the days exceeding the environmental standard for just 2 hours. The average number of asthma-related hospital visits peaked on the third day after the event. Asthma-related hospitalizations also increased on the third day after the event. Children and older adults were found to be particularly vulnerable to the effects of PM exposure.

Although PM exposure and its associated respiratory health hazards are common concerns for everyone, vulnerable populations, such as individuals with chronic respiratory illnesses, are particularly at an increased risk. Asthma is a common chronic airway inflammatory disease affecting 1–18% of the population in different countries.¹¹ Although there have been a number of studies on the effects of short-term PM exposure on asthma exacerbations, the extent of the effects varies depending on the distribution of susceptible or vulnerable populations, the composition of PM, and the environmental standards and policies of each country.

Most previous studies used concentration-response functions (CRFs; the percent change in a given health outcome per $\mu g/m^3$ change in concentrations) to assess risk; however, to assess the effect of short-term exposure to PM exceeding the current environmental standard on asthma exacerbations, we investigated the average number of asthma-related hospital visits from the day exceeding the daily average environmental standard for PM₁₀ and PM_{2.5} to 5 days after the event day. The daily average environmental standards of Korea are ≤100 µg/m³ for PM_{10} and $\leq 50 \ \mu g/m^3$ for $PM_{2.5}$, which are higher than the WHO Air Quality Guidelines.¹² However, there is no evidence for which level of exposure is safe.¹² In this study, the average number of asthma-related hospital visits on the days exceeding the daily average environmental standard for PM₁₀ and PM_{2.5} increased by 4.10% and 5.66%, respectively. In addition, while outpatient visits primarily increased, emergency room visits also increased on the 2-hr event days for PM_{2.5}. This suggests that PM_{2.5} has a greater impact on asthma exacerbations than PM₁₀ and is associated with more severe asthma exacerbations. In a recent meta-analysis of case-crossover studies, PM₁₀ was also not associated with increased emergency room visits or hospitalizations, whereas PM2.5 was.8 However, this meta-analysis did not evaluate outpatient visits because most included studies were conducted in North America and Europe where outpatient visits are generally scheduled by appointment, leading most patients with asthma exacerbations to primarily use the emergency room. Therefore, these studies do not reliably reflect the true morbidity and offer an opportunity to examine the association between short-term PM exposure and overall asthmarelated hospital visits. Among the studies that did include outpatient visits, a population-based study in Taiwan also showed that as PM_{10} concentration increased, outpatient visits due to asthma increased, whereas the risk for emergency room visits and hospitalizations did not increase.¹³ However, another recent study in China showed that every 10 µg/m³ increase in $PM_{2.5}$ concentration was significantly associated with an increase in outpatient visits and emergency room visits on the same day.¹⁴ It is not yet clear whether the reason for the difference between these studies is due to the size of PM. In addition to PM size, the difference in the severity of the asthma patients included and the medical system, including medical insurance, in each country may also be associated.

In this study, we noted a slight difference in asthma-related hospital visits after PM exposure among regions (Supplementary Tables 1–5, online only). We assume that various factors, including the composition of PM, the severity of asthma, and socioeconomic factors, are involved. Further research is needed to clarify this.

In this study, we noted a time lag (measured in days) between short-term PM exposure and asthma exacerbations. Asthmarelated hospital visits increased beginning the day when PM₁₀ or PM_{2.5} exceeded the daily average environmental standard, peaked on the third day after the event, and then decreased. Hospitalizations that could be considered as a moderate to severe deterioration of asthma also increased on the third day after the event. Previous studies have also described a time lag of 0-4 days, suggesting that PM is not simply acting as an airway irritant.7,15 In experimental studies using animal models and in vitro airway epithelial cells, a cause-and-effect relationship between ambient PM₁₀ and asthma exacerbation was demonstrated via oxidative stress, with release of interleukin-33.16,17 In addition, human airway epithelial cells exposed to PM expressed inflammatory cytokines.¹⁸ Although the mechanism by which PM induces asthma exacerbation is not well known, these results suggest that PM can cause asthma symptoms through induction and aggravation of airway inflammation. The time lag from PM exposure to hospital visits can also be partially explained by these results.

One reason for various time lags in individual studies may be variations in asthma severity in the study population. If a study includes a large number of patients with moderate to severe asthma, the time lag may be shorter than in studies including predominantly mild patients. However, most studies, including this study, did not include the asthma severity of their study population in the analysis due to limitations in the data used. Another reason may be the difference in composition of PM. The composition of PMs varies depending on the primary emission source and the weather conditions in each country or region.^{2,19} Several studies reported that the health effects of PM are different depending on their composition.²⁰ However, which constituents of PM have a major influence on the deterioration of asthma remains to be elucidated, and this should be clarified in order to correctly understand and reduce the health effects of PM.

What is interesting to note in this study is that even after exposure to PM₁₀ or PM₂₅ exceeding the environmental standard for a very short period of time, the number of asthma-related hospital visits increased. Although they increased less than on the day exceeding the daily average environmental standard, asthma-related hospital visits significantly increased even on the day exceeding the environmental standard for only 2 hours. Although the short time lag (1-6 hours) from PM_{10-2.5} exposure to asthma-related emergency department visits in a recent study suggested the possibility that asthma exacerbation could occur even after exposure to an hourly increase in PM₁₀, this is the first study to confirm the effects of exposure to increased PM over several hours on asthma-related hospital visits. Unlike hourly average environmental standards for other air pollutants, there are no countries that set hourly average environmental standards for PM, except Japan.²¹ Although it will need to be verified by other studies, the results of this study suggest that it may be necessary to establish hourly average environmental standards for PM just as for other air pollutants.

In the present study, the effect of $PM_{2.5}$ on asthma-related hospital visits on the event day was more prominent than that of PM_{10} , although thereafter, the effect was less than that of PM_{10} . This is in contrast to a recent study from Hong Kong that reported a more delayed observable response after $PM_{2.5}$ exposure.²¹ One reason for this discrepancy may be a difference in the composition of PM as described above. Therefore, it is necessary to establish a nationwide monitoring network by increasing the number of monitoring stations and evaluate the composition of PM in parallel.

Many recent studies have focused on the association between $PM_{2.5}$ exposure and asthma exacerbation based on results indicating that the influence of $PM_{2.5}$ is greater than that of PM_{10} , thus neglecting the effects of $PM_{2.5-10}$, which is included in PM_{10} . However, an experimental study demonstrated that PM_{10} causes more damage to airway epithelial cells than $PM_{2.5}$, which is explained by the ionic component contained in PM_{10} .²² These findings suggest that studies or policies on the assessment of health effects of PM should not be limited to $PM_{2.5}$.

In this study, the effects of PM exposure on asthma exacerbations were more pronounced in children and older adults, which is consistent with previous findings.^{23,24} However, the effect on adolescents was significantly higher when compared to other studies. This seems to be due to the fact that in this population, compliance with parental and school instructions, such as reduction of outdoor activities and mask use on days of high ambient PM concentrations, is low compared to younger children.

Asthma-related hospital visits on the event day varied according to insurance type in this study. Although the government pays medical expenses for patients covered by medical aid in Korea, asthma-related hospital visits on the event day did not increase in the medical aid group, unlike the health insurance group. This is likely due to differences in health behavior and use of medical institutions among different socioeconomic groups, rather than differences in the effect of PM on asthma exacerbation depending on insurance type.²⁵

This study has several strengths. First, this is a nationwide study that evaluated the short-term effects of PM on asthmatic patients, including outpatient visits, as well as emergency room visits and hospitalizations, based on the latest NHI data. Second, in order to increase the reliability of actual hospital visits due to asthma, a working definition, which included the prescription of asthma medication along with the ICD-10 codes, was applied. Finally, we assessed the effect of very short-term PM exposure (2 hours) on asthma exacerbation for the first time.

Several potential limitations of this study should be taken into consideration. First, among the outpatient visits due to asthma, we could not exclude patients who visited clinics for regular follow up. However, given that the event day and the control day were the same day of the week at a 7 day interval, the number of patients visiting clinics for regular follow up could be estimated to be similar, so their possible effect may be negligible. Although seasons or viral epidemics can affect asthma exacerbations, for the same reason, we think their effects were also negligible. Second, PM_{2.5} data were collected from a relatively small number of monitoring stations, compared to PM₁₀, which can cause an exposure measurement error and underestimate the effects of PM_{2.5}.²⁶ In addition, since the composition of PM is not vet monitored in Korea, the influence of PM composition cannot be analyzed. Third, because of the limited data available, the impact of other air pollutants, such as sulfur dioxide, nitrogen dioxide, carbon monoxide, and ozone, could not be appropriately adjusted for. Although the levels of sulfur dioxide and carbon monoxide on the event days were slightly higher than that on control days, their possible effect would not be significant since the levels were far below the current daily average environmental standard (see supplementary materials for details). However, additional studies are warranted to examine the independent effect of PM on asthma.

In conclusion, we found a significant association between short-term PM exposure exceeding the current daily average environmental standard and asthma-related hospital visits. This association was also observed even after PM exposure exceeded the current environmental standard for just 2 hours. To our knowledge, this is the first study to assess the impact of PM exposure on asthmatic patients based on the daily average environmental standard. Although further studies investigating the actual harmful constituents of particulates and time course of PM induced effects are needed to better understand the effects of PM exposure on asthma, these results are expected to contribute to the establishment of appropriate environmental standards and relevant policies for PM. In addition to implementing effective policies to reduce ambient PM levels, accurate forecasts based on a nationwide monitoring network and continuous publicity and education are important for preventing and minimizing the harmful effects of PM on asthma exacerbation.

ACKNOWLEDGEMENTS

This study was supported by grant from the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI) and the Korea Asthma Allergy Foundation (KAF). National Health Information Data were provided by the National Health Insurance Service (NHIS) of Korea.

AUTHOR CONTRIBUTIONS

Conceptualization: Dae Jin Song, Sang-Heon Cho, and Dae Hyun Lim. Data curation: Dae Jin Song. Formal analysis: Dae Jin Song and Dae Hyun Lim. Funding acquisition: Dae Hyun Lim. Investigation: Dae Jin Song and Dae Hyun Lim. Methodology: All authors. Project administration: Dae Hyun Lim. Resources: Dae Hyun Lim. Software: Dae Jin Song and Dae Hyun Lim. Supervision: Sang-Heon Cho and Dae Hyun Lim. Validation: Dae Jin Song and Dae Hyun Lim. Visualization: Dae Jin Song and Dae Hyun Lim. Writing—original draft: Dae Jin Song. Writing—review & editing: Sun Hee Choi, Woo-Jung Song, Kyung Hee Park, Young-Koo Jee, Sang-Heon Cho, and Dae Hyun Lim.

ORCID iDs

Dae Jin Song Sun Hee Choi Woo-Jung Song Kyung Hee Park Young-Koo Jee Sang-Heon Cho Dae Hyun Lim https://orcid.org/0000-0003-0647-3186 https://orcid.org/0000-0002-0554-2250 https://orcid.org/0000-0002-4630-9922 https://orcid.org/0000-0003-3605-5364 https://orcid.org/0000-0001-5800-8038 https://orcid.org/0000-0002-7644-6469 https://orcid.org/0000-0002-4558-3284

REFERENCES

- 1. Brunekreef B, Holgate ST. Air pollution and health. Lancet 2002; 360:1233-42.
- Bell ML, Dominici F, Ebisu K, Zeger SL, Samet JM. Spatial and temporal variation in PM(2.5) chemical composition in the United States for health effects studies. Environ Health Perspect 2007; 115:989-95.
- Song WJ, Wong GWK. Changing trends and challenges in the management of asthma in Asia. J Allergy Clin Immunol 2017;140: 1272-4.
- 4. Kang D, Kim JE. Fine, ultrafine, and yellow dust: emerging health problems in Korea. J Korean Med Sci 2014;29:621-2.
- Leung TF, Ko FW, Wong GW. Roles of pollution in the prevalence and exacerbations of allergic diseases in Asia. J Allergy Clin Immunol 2012;129:42-7.
- Park M, Luo S, Kwon J, Stock TH, Delclos G, Kim H, et al. Effects of air pollution on asthma hospitalization rates in different age groups in metropolitan cities of Korea. Air Qual Atmos Health 2013;6: 543-51.
- Zheng XY, Ding H, Jiang LN, Chen SW, Zheng JP, Qiu M, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: a systematic review and meta-analysis. PLoS One 2015;10:e0138146.
- Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. PLoS One 2017;12:e0174050.

- 9. Bae S, Kwon HJ. Current state of research on the risk of morbidity and mortality associated with air pollution in Korea. Yonsei Med J 2019;60:243-56.
- 10. Kim J, Kim H, Kweon J. Hourly differences in air pollution on the risk of asthma exacerbation. Environ Pollut 2015;203:15-21.
- 11. World Health Organization (WHO) Regional Office for Europe. Air quality guidelines global updates 2005 [Internet]. Copenhagen: WHO Regional Office for Europe; c2016 [accessed on 2017 November 19]. Available at: http://www.euro.who.int/__data/assets/pdf_file/0005/78638/E90038.pdf?uaZ1.
- 12. World Health Organization (WHO) Regional Office for Europe. Health effects of particulate matter. Policy implications for countries in eastern Europe, Caucasus and central Asia [Internet]. Copenhagen: WHO Regional Office for Europe; c2013 [accessed on on 2017 November 19]. Available at: http://www.euro.who.int/__ data/assets/pdf_file/0006/189051/Health-effects-of-particulatematter-final-Eng.pdf.
- Pan HH, Chen CT, Sun HL, Ku MS, Liao PF, Lu KH, et al. Comparison of the effects of air pollution on outpatient and inpatient visits for asthma: a population-based study in Taiwan. PLoS One 2014;9:e96190.
- 14. Tian Y, Xiang X, Juan J, Sun K, Song J, Cao Y, et al. Fine particulate air pollution and hospital visits for asthma in Beijing, China. Environ Pollut 2017;230:227-33.
- Lim H, Kwon HJ, Lim JA, Choi JH, Ha M, Hwang SS, et al. Shortterm effect of fine particulate matter on children's hospital admissions and emergency department visits for asthma: a systematic review and meta-analysis. J Prev Med Public Health 2016;49: 205-19.
- 16. Herbert C, Siegle JS, Shadie AM, Nikolaysen S, Garthwaite L, Hansbro NG, et al. Development of asthmatic inflammation in mice following early-life exposure to ambient environmental particulates and chronic allergen challenge. Dis Model Mech 2013;6:479-88.
- 17. Shadie AM, Herbert C, Kumar RK. Ambient particulate matter induces an exacerbation of airway inflammation in experimental asthma: role of interleukin-33. Clin Exp Immunol 2014;177:491-9.
- 18. Silbajoris R, Osornio-Vargas AR, Simmons SO, Reed W, Bromberg PA, Dailey LA, et al. Ambient particulate matter induces interleukin-8 expression through an alternative NF-kB (nuclear factor-kappa B) mechanism in human airway epithelial cells. Environ Health Perspect 2011;119:1379-83.
- 19. Son JY, Lee JT, Kim KH, Jung K, Bell ML. Characterization of fine particulate matter and associations between particulate chemical constituents and mortality in Seoul, Korea. Environ Health Perspect 2012;120:872-8.
- Bell ML, Ebisu K, Peng RD, Samet JM, Dominici F. Hospital admissions and chemical composition of fine particle air pollution. Am J Respir Crit Care Med 2009;179:1115-20.
- Pun VC, Tian L, Yu IT, Kioumourtzoglou MA, Qiu H. Differential distributed lag patterns of source-specific particulate matter on respiratory emergency hospitalizations. Environ Sci Technol 2015;49:3830-8.
- 22. Kumar RK, Shadie AM, Bucknall MP, Rutlidge H, Garthwaite L, Herbert C, et al. Differential injurious effects of ambient and traffic-derived particulate matter on airway epithelial cells. Respirology 2015;20:73-9.
- 23. Fan J, Li S, Fan C, Bai Z, Yang K. The impact of PM2.5 on asthma emergency department visits: a systematic review and meta-analysis. Environ Sci Pollut Res Int 2016;23:843-50.
- 24. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. Am J Epidemiol 2013;178:865-76.

- 25. Park YS, Kim JH, Jang HJ, Tae YH, Lim DH. The effect of Asian dust on asthma by socioeconomic status using national health insurance claims data in Korea. Inhal Toxicol 2016;28:1-6.
- 26. Goldman GT, Mulholland JA, Russell AG, Strickland MJ, Klein M,

Waller LA, et al. Impact of exposure measurement error in air pollution epidemiology: effect of error type in time-series studies. Environ Health 2011;10:61.