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Epidemiological Studies on Health Effects of Fine Particulate Matter (PM_{2.5}) in Japan

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Abstract

To evaluate the short-term effects of fine particulate matter (PM_{2.5}) on respiratory health, epidemiological studies were conducted in two regions around the Seto Inland Sea in Japan. In Himeji City, Hyogo Prefecture, weekly data on asthma attacks reported from 46 hospitals and clinics and daily data on primary care visits (PCVs) due to asthma attacks were collected. The mass concentrations and chemical constituents of airborne $PM_{2.5}$ were continuously measured at a central site in the city. The weekly numbers of asthma attacks were significantly associated with the average concentration of $PM_{2.5}$ in the previous week among subjects aged 15 to 64 years. The concentration of water soluble organic carbon and acidity (hydrogen ions) were also significantly associated with weekly asthma attacks. These associations were marked in spring and summer. By contrast, the associations between daily PCVs for asthma and PM_{25} were significant in winter. On Yuge Island, Ehime Prefecture, peak expiratory flow (PEF) and the forced expiratory volume in 1 second (FEV_1) were measured every morning among 48 healthy students, for about one month. Among subjects with a history of allergies, outdoor concentration of PM_{2.5} was significantly associated with a decrease in FEV1. The association between indoor concentration of PM2.5 and PEF was also significant. However, among subjects without such a history, neither outdoor nor indoor concentrations of $PM_{2.5}$ were associated with changes in any parameters of pulmonary function. In conclusion, these studies revealed that increases of PM_{2.5} have short-term effects on respiratory health. Subjects with allergic diseases were considered to be more susceptible to air pollution.

Key words : asthma attacks, epidemiology, fine particulate matter $(PM_{2.5})$, ozone (O_3) , pulmonary function, primary care visits

1. Introduction

The World Health Organization (WHO) (2018) estimated that ambient air pollution caused around 4.2 million premature deaths worldwide in 2016. This mortality is presumed to be mainly due to exposure to fine particulate matter of 2.5 μ m or less in diameter (PM_{2.5}), which causes respiratory and cardiovascular diseases, and cancers. Therefore, the WHO recognizes that air pollution including PM_{2.5} is the greatest risk to human health. Many epidemiological studies have been conducted worldwide, and the adverse health effects of PM_{2.5} on morbidity and mortality due to respiratory and cardiovascular diseases have been reported in many countries.

In Japan, several epidemiological studies were conducted on acute and chronic health effects of exposure to $PM_{2.5}$ by study groups established by the Ministry of the Environment of Japan (MOEJ) from 1999 to 2006, and the reports on this research were released in 2007 (MOEJ, 2007). Since then, we have

conducted another epidemiological study to evaluate the short-term effects of exposure to $PM_{2.5}$ on respiratory health among asthmatic children (Ma *et al.*, 2008). Thereafter, in order to investigate the effects of exposure to $PM_{2.5}$ and ozone (O₃) on respiratory health, we have performed some epidemiological studies in two regions around the Seto Inland Sea of Japan, under the Environment Research and Technology Development Fund (ERTDF) (Project No. 5–1456).

In this paper, the epidemiological studies on health effects of $PM_{2.5}$ conducted by the MOEJ in the past in Japan are reviewed, and the results of our studies, which were conducted under the ERTDF, are referred to.

2. Epidemiological Studies by the MOEJ Study Group

The MOEJ study group conducted several epidemiological studies to evaluate the effects of shortand long-term exposures to $PM_{2.5}$ on mortality and morbidity from respiratory and cardiovascular diseases

 Table 1
 Summary of the results of epidemiological studies on health effects of particulate matter (PM) by Ministry of the Environment of Japan study groups.

Outcome		Effects of PM	Main results						
Study on the effects of exposure to fine particulate matter (2007)									
Short-term ex	posure								
Mortality	All-cause	\bigtriangleup	The risk rose slightly in relation to $PM_{2.5}$ concentrations.						
	Respiratory	\bigcirc	The risk rose significantly in relation to $PM_{2.5}$ concentrations for 3 lag days.						
	Cardiovascular	×	No association with PM _{2.5} was observed.						
Morbidity	Physician visits	×	Asthma-related primary care visits were not associated with PM _{2.5} concentrations.						
	Respiratory	\bigcirc	Peak expiratory flow (PEF) decreased significantly in relation to increased $PM_{2.5}$ concentrations among asthmatic children. In healthy children, a slight decrease in PEF was also observed in relation to $PM_{2.5}$.						
	Cardiovascular	×	No association between ventricular arrhythmia and SPM concentrations was observed.						
Long-term exposure									
	Respiratory		$PM_{2.5}$ concentrations were related to neither prevalence nor incidence of respiratory symptoms among children aged 3 to 7 years. The prevalences of cough and phlegm among their parents were higher in areas with high $PM_{2.5}$ concentrations than in areas with low concentrations.						
Study on the	effects of long-ter	n exposur	e to ambient particulate matter (2009)						
	All-cause	×	No association with air pollutants was observed.						
	Lung cancer	\bigcirc	Lung cancer mortality was significantly associated with SPM, SO ₂ and NO ₂ , after adjustment for smoking and other confounding factors.						
	Respiratory	\bigtriangleup	Significant associations with SO_2 , and NO_2 were observed among females, but the association with SPM was not significant.						
	Cardiovascular	×	Significant negative association with SPM was observed, although confounding factors including blood pressure were not adjusted.						

 $PM_{2.5}$, particulate matter \leq 2.5 μ m in diameter; SPM, suspended particulate matter; SO_2 , sulfur dioxide; NO_2 , nitrogen dioxide.

 \bigcirc : Significant associations with PM_{2.5} or SPM were observed.

 \triangle : Associations with PM_{2.5} or SPM were suggested, but not necessarily clarified.

× : No associations with PM2.5 or SPM were observed.

from 1999 to 2006. The main subjects of these studies were chosen in view of the health effects observed in previous studies in the United States and European countries. The main results of these studies are summarized in Table 1. In some of the studies, the effects of suspended particulate matter (SPM) were evaluated as a surrogate for PM_{2.5}, because data on the concentrations of PM_{2.5} were unavailable in the study areas. In Japan, SPM is defined as particles with an aerodynamic diameter of $\leq 10 \,\mu\text{m}$ by the 100% cutoff point, which corresponds approximately to PM_{7.0} by the 50% cutoff point.

In the study on the mortality in 20 cities in Japan, the daily all-cause mortality risk rose slightly in relation to increases in daily average concentrations of $PM_{2.5}$, but the risk was not significant. The daily risk of mortality due to respiratory diseases rose significantly in relation to $PM_{2.5}$ concentrations with a lag of three days. However, mortality due to cardiovascular diseases was not associated with $PM_{2.5}$ concentrations after any number of lag days, although many studies in foreign countries have reported effects of $PM_{2.5}$ on mortality due to cardiovascular diseases.

For short-term respiratory morbidity, a panel study was conducted to evaluate the association between exposure to $PM_{2.5}$ and peak expiratory flow (PEF)

among 17 children aged 8 to 15 years hospitalized with severe asthma (Yamazaki et al., 2011). PEF was measured twice daily for three months, and a total of 1,198 and 1,175 measurements were performed at 7 a.m. and 7 p.m., respectively. The changes in PEF were estimated in 10 μ g/m³ increments of PM_{2.5}, after adjustment for sex, age, height and temperature. Increased 24-hr. mean concentration of PM25 was associated with a decrease in both morning and evening PEF (-3.0 L/min [95% confidence interval (CI) : -4.6,-1.4] and -4.4 L/min [-7.1, -1.7], respectively). In addition, lagged-hour exposures of up to 24 hours were examined. Hourly concentrations of PM2.5 showed significant associations with PEF at several lags. The effect size was about -3 L/min in both morning and evening PEF for an hourly PM2.5 concentration of $10 \,\mu\text{g/m}^3$ (Fig. 1). Even after adjustment for other air pollutants, many of the significant associations with PEF remained. That is, increased hourly PM2.5 concentration was associated with a decrease in PEF among children hospitalized with severe asthma.

In another panel study of healthy children aged 9-10 years, a slight decrease in PEF was also observed in relation to increased $PM_{2.5}$ concentrations. Primary care visits (PCVs) due to asthma attack, however, were not associated with $PM_{2.5}$ concentrations, although O_3

concentrations were significantly associated with PCVs for asthma attack (Yamazaki *et al.*, 2009). As for cardiovascular effects, no association between ventricular arrhythmia and SPM concentrations was observed.

A cohort study was conducted to evaluate the effects of long-term exposure to $PM_{2.5}$. Respiratory symptoms among children aged three years and their parents in seven regions of Japan were surveyed every year for five years. The annual averages of $PM_{2.5}$ concentrations during the follow-up period were related to neither prevalence nor incidence of respiratory symptoms among children from three to seven years in age. On the other hand, the prevalences of coughing and phlegm among their parents were higher in areas with high $PM_{2.5}$ concentrations.

Another prospective cohort study was conducted by the MOEJ to evaluate the effects of long-term exposure to ambient particulate matter on mortality. This study comprised 63,520 participants living in six areas in three Japanese prefectures who were enrolled between 1983 and 1985. During the average follow-up period of 8.7 years, 6,687 deaths, including 518 deaths from lung cancer, were observed (Katanoda *et al.*, 2011). Although all-cause mortality was not associated with any air pollutant, the mortality due to lung cancer was significantly associated with SPM, sulfur dioxide (SO_2) , and nitrogen dioxide (NO_2) , after adjustment for smoking and other confounding factors. This finding was consistent with the results of previous studies in the United States and European countries. In addition, the mortality due to respiratory diseases, in particular pneumonia, was significantly associated with SO₂ and NO₂, but only among females, and the association with SPM was not significant. On the other hand, mortality due to cardiovascular diseases was negatively associated with SPM concentrations, although confounding factors including blood pressure were not adjusted.

In summary, the results of the studies conducted by the MOEJ study group suggested adverse effects of $PM_{2.5}$ or SPM on the respiratory system among Japanese. No effect on the cardiovascular system was observed, however. Further studies are thought necessary for a more detailed evaluation of the health effects of $PM_{2.5}$.

3. Epidemiological Studies on Effects of PM_{2.5} and O₃ on Respiratory Health in Areas with Different Air Pollution Levels

In order to evaluate the short-term effects of $PM_{2.5}$ and O_3 on respiratory health, several epidemiological



Fig. 1 Association of peak expiratory flow (PEF) measured in (a) morning and (b) evening with hourly concentrations of $PM_{2.5}$. Lagged-hour exposures of up to 24 hours were examined. The mean differences and 95% confidence intervals in PEF per $10 \,\mu\text{g/m}^3$ increases in $PM_{2.5}$ were estimated.

studies were conducted in two regions (Himeji City, Hyogo Prefecture; and Yuge Island, Ehime Prefecture) which are located around the Seto Inland Sea (Fig. 2).

3.1 Effects on Asthma Attacks in Himeji City

Short-term exposure to ambient $PM_{2.5}$ has been reported to be associated with morbidity from asthma in many previous studies. The association with chemical constituents of $PM_{2.5}$, however, is still uncertain. The main purpose of this study was to evaluate the short-term effects of chemical constituents in airborne $PM_{2.5}$ on asthma attacks. This study was conducted in Himeji City, Hyogo Prefecture, Japan, which is located on the north side of the Seto Inland Sea (Fig. 2). The city is 534.4 km² in area, and its population is about 540,000. Steel mills, thermal power plants and chemical facilities are located in the southern coastal part of the city (Nakatsubo *et al.*, 2014).

We collected weekly data on patients with asthma attacks reported from 46 hospitals and clinics in eight districts of the city from 2012 to 2017. An asthma attack is defined as dyspnea with wheezing and/or whistling sounds, and is confirmed through medical examinations, inquiries and symptom diaries. Regular visits due to asthma were excluded. Mass concentrations of $PM_{2.5}$ were continuously measured at seven sites in the city.

The chemical constituents of $PM_{2.5}$ were also measured from July 2014 to March 2017 at a central site in the city, using a dichotomous aerosol chemical speciation analyzer (ACSA-14, Kimoto Electric Co., Ltd., Japan). The association between the weekly number of patients who had asthma attacks in each district and the mass concentrations of airborne $PM_{2.5}$ in each respective district was analyzed using the mixed effect model, after adjustment for meteorological factors. In addition, the associations between the weekly number of patients with asthma attacks and concentrations of chemical constituents in $PM_{2.5}$ were analyzed using generalized linear models.

The total number of patients with asthma attacks during the study period was 57,327, and the weekly number varied from 156 to 331. The average mass concentration of $PM_{2.5}$ during the period was 14.3 µg/m³, and it was less than air quality standard for annual average of $PM_{2.5}$ in Japan. Daily concentrations of chemical constituents in $PM_{2.5}$ from July 2014 to March 2017 are shown in Table 2.

The weekly numbers of asthma attacks were significantly associated with the average mass concentrations of $PM_{2.5}$ in the previous week, and the relative risk (RR) was 1.18 [95% CI: 1.05, 1.31] per 10 µg/m³ increment. Although the RR was 0.88 [0.66,



Fig. 2 Location of Himeji City and Yuge Island around the Seto Inland Sea, Japan.



Fig. 3 Association between weekly asthma attacks and $PM_{2.5}$ concentrations, in relation to age.

The data are relative risks and 95% confidence intervals associated with 10 μ g/m³ increases in average PM_{2.5} concentrations in the previous week, adjusted for temperature, relative humidity, atmospheric pressure and hours of daylight.

 Table 2 Descriptive statistics on daily concentrations of mass and chemical constituents in PM_{2.5} from July 2014 to March 2017.

	n	Mean	SD	Maximum	Minimum	IQR
$PM_{2.5} \ (\mu g/m^3)$	972	12.6	6.6	39.2	1.5	5.2
SO_4^{2-} (µg/m ³)	909	3.49	2.34	15.8	0.03	2.12
NO_3^{-} (µg/m ³)	929	1.19	1.06	7.50	0.06	1.12
WSOC (µg/m ³)	929	0.86	0.56	3.67	0.05	0.54
Acidity $[H^+]$ (nmol/m ³)	872	7.55	6.43	56.7	0.26	4.51

SD: standard deviation; IQR: interquartile range; $PM_{2,5}$: particulate matter $\leq 2.5 \,\mu m$ in diameter; $SO_4^{2^-}$: sulfate ion; NO_3^- : nitrate ion; WSOC: water soluble organic carbon; H^+ : hydrogen ion.



Fig. 4 Association between weekly asthma attacks and chemical constituents in PM_{2.5}, in relation to (a) age and (b) season.

The data are relative risks and 95% confidence intervals associated with interquartile range (IQR) increases in the average concentrations of chemical constituents in $PM_{2.5}$ in the previous week, adjusted for temperature, relative humidity, atmospheric pressure and hours of daylight. The IQR of each chemical constituent in $PM_{2.5}$ is shown in Table 2.

1.10] among children aged 0-4 years, RR increased with advancing age. It was significant among groups aged over 10 years, and the largest RR was 1.33 [1.15, 1.51] among elderly subjects aged 65 years or above (Fig. 3).

For chemical constituents in $PM_{2.5}$, the concentration of water soluble organic carbon (WSOC) and acidity (hydrogen ion (H^+)) in the previous week were significantly associated with increased weekly numbers of asthma attacks among subjects aged 15–64 years (Fig. 4 (a)). The RRs were 1.07 [1.02, 1.12] and 1.04 [1.01, 1.07] for interquartile range (IQR) increments of WSOC (0.54 µg/m³) and H⁺ (4.51 nmol/m³), respectively.

The associations between weekly asthma attacks and chemical constituents in $PM_{2.5}$ varied according to the season (Fig. 4 (b)). Weekly asthma attacks were significantly associated with concentrations of nitrate ion (NO_3^{-}) and WSOC in spring and H⁺in summer (RRs = 1.05 [1.02, 1.08], 1.05 [1.01, 1.10] and 1.09 [1.01, 1.17], respectively, for IQR increments). No significant

association was observed between sulfate ion (SO_4^{2-}) and asthma attacks in any season.

Thus, the results obtained in this study showed that weekly asthma attacks increased in relation to increments in ambient $PM_{2.5}$ concentrations in the previous week. The associations between chemical constituents in $PM_{2.5}$ and asthma attacks varied among age groups and seasons. The associations with NO_3^- and WSOC in spring may reflect the effects of transboundary air pollution from East Asia. On the other hand, concentrations of H^+ in $PM_{2.5}$ are usually high in summer. Acid chemical constituents, such as WSOC and H^+ , in ambient $PM_{2.5}$ may have more effects on exacerbation of asthma in patients.

3.2 Effects on Primary Care Visits (PCVs) due to Asthma Attacks in Himeji City

The association between daily outdoor air pollution concentrations and children's PCVs at night due to asthma attack was examined in Himeji City, Hyogo

Table 3	Associations h	between air polluta	nts and PCVs at nig	ht due to asthma attack	(multi-pollutant model).
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	Unit increment	Spring (April through June)		Summer (July and August)		Fall t No	Fall (September through November)			Winter (December through March)			Annual effects			
		OR	95%	6 CI	OR	95%	6 CI	OR	95%	6 CI	OR	95%	6 CI	OR	95%	6 CI
Concentration on the day before a primary care visit																
PM _{2.5}	10 µg/m ³	0.95	0.85	1.06	1.17	0.98	1.40	0.96	0.86	1.06	1.16*	1.01	1.33	1.02	0.96	1.08
O_3	10 ppb	1.17*	1.01	1.35	1.09	0.93	1.27	0.98	0.80	1.20	1.22	0.81	1.83	1.12*	1.03	1.21
NO_2	10 ppb	1.16	0.83	1.62	0.76	0.38	1.53	1.17	0.80	1.72	0.86	0.49	1.51	0.98	0.81	1.18
3-day mean concentration before a primary care visit																
PM _{2.5}	10 µg/m ³	0.95	0.82	1.10	1.13	0.88	1.45	0.92	0.80	1.05	1.15	0.95	1.38	0.99	0.92	1.07
O_3	10 ppb	1.21*	1.00	1.46	1.12	0.90	1.41	0.99	0.75	1.30	1.25	0.73	2.13	1.16*	1.04	1.29
NO_2	10 ppb	1.04	0.68	1.58	0.58	0.20	1.71	1.17	0.72	1.90	0.67	0.33	1.35	0.90	0.71	1.14

The analysis was performed using a model which simultaneously assessed the associations between PCVs at night due to asthma attack and increments of PM_{2.5}, O₃ and NO₂.

Associations are shown as odds ratios (ORs) and their 95% confidence intervals (CIs) per unit increment of each parameter.

PCV: primary care visit; $PM_{2.5}$: particulate matter $\leq 2.5 \,\mu m$ in diameter; O_3 : ozone; NO_2 : nitrogen dioxide; **Bold** and *: p < 0.05.

Prefecture (Yamazaki et al., 2013, 2014, 2015).

This study was conducted at the Himeji City Emergency Clinic, using a case-crossover design for three-year pooled patients. Subjects were city residents aged less than 15 years with a history of asthma attacks who visited the clinic for asthma attacks between 9 p.m. and 6 a.m. from April 2010 to March 2013 and who had received a prescription for bronchodilators from their primary care physician. In Himeji City, primary care at night is generally only available at this emergency clinic, and almost all patients who suffer asthma attacks at night visit the clinic. Daily concentrations of air pollutants and meteorological parameters were measured at a site central to the residential districts in the city. A conditional logistic regression model including PM_{25} , O_3 , and NO_2 was used to estimate odds ratios (ORs) of PCVs per unit increment of air pollutants (the per-unit increments of $PM_{2.5}$, O_3 and NO_2 were 10 µg/m³, 10 ppb and 10 ppb, respectively), after adjustment for meteorological parameters. Analyses took into consideration the effects of seasonality.

In a year-round analysis, significant associations were observed between PCVs due to asthma attacks and daily (day before a PCV) and three-day mean concentrations of O₃ before a PCV (ORs = 1.12 [95% CI: 1.03, 1.21] and 1.16 [1.04, 1.29], respectively). Neither daily nor three-day mean concentration of PM_{2.5}, however, was associated with PCVs.

The results of seasonal analyses are shown in Table 3. The association between PCVs and O_3 concentrations on the day before a PCV was significant (OR = 1.17 [1.01, 1.35]) in spring. In addition, the association between PCVs and three-day mean O_3 concentrations before a PCV was also significant (OR = 1.29 [1.00, 1.46]) in spring. We also observed a significant association between PCVs and PM_{2.5} concentrations on the day before a PCV in winter (OR = 1.16 [1.01, 1.33]). No association between three-day mean PM_{2.5} concentrations and PCVs, however, was observed in any

season. By contrast, PCVs were not associated with any NO_2 concentration.

In this way, the findings of this study showed that PCVs due to asthma attacks were associated with O_3 concentrations in spring and $PM_{2.5}$ concentrations in winter. The association with O_3 was also significant in a year-round analysis. There may be seasonal variation in effects of air pollutants on PCVs.

3.3 Short-term Effects on Pulmonary Function among Students: a Panel Study on Yuge Island

In the past, many epidemiological studies on the health effects of air pollutants have been carried out in regions with major sources such as factories and automobiles. On the other hand, the health effects of air pollutants in regions without major sources remain unclear. This study investigated the short-term effects of ambient air pollution on pulmonary function among healthy students on an isolated island without major anthropogenic sources of air pollutants (Yoda *et al.*, 2015, 2017).

A panel study was conducted among 48 healthy subjects who attended a school on Yuge Island, Ehime Prefecture, an isolated island in the Seto Inland Sea, Japan (Fig. 2). For pulmonary function testing, an electronic peak flow meter (Vitalograph 2110, Vitalograph Ltd., Buckingham, U. K.) was delivered to each subject, and self-measurement of peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1) was conducted before the start of the first lesson every morning from Monday until Friday, for about one month. Ambient concentrations of PM2.5, particulate matter between 2.5 and 10 μ m in diameter (PM_{10-2.5}), black carbon (BC), O_3 and NO_2 were measured. The associations between the concentrations of air pollutants and pulmonary function were analyzed using mixedeffects models.

The mean \pm SD of daily outdoor and indoor concentrations of PM_{2.5} were $30.9 \pm 12.5 \,\mu\text{g/m}^3$ and 17.0





 \pm 9.6 µg/m³, respectively. The maximum outdoor daily concentration of PM_{2.5} was 61.6 µg/m³, which was measured on a day on which a dust storm from China arrived in Japan. On the same day, the concentration of PM_{10-2.5} was also high (53.8 µg/m³).

A decrease in FEV₁ was significantly associated with an increase in the prior 24–hr. average concentration of BC (-27.28 mL [95% CI: -54.10, -0.46] for an IQR increase of 0.23 µg/m³). A decrease in PEF was significantly associated with an increase in the prior 24–hr. average concentration of indoor O₃ (-8.03 L/min [-13.02, -3.03] for an IQR increase of 11.0 ppb). Neither outdoor nor indoor concentration of PM_{2.5} was significantly associated with changes in any pulmonary function parameters.

The associations between concentrations of air pollutants and pulmonary function parameters were analyzed with respect to the presence or absence of a history of asthma or allergies (Fig. 5). Among subjects with a history of allergies, PEF decreased significantly with an increase in the indoor concentration of $PM_{2.5}$ (-6.71 L/min [-13.36, -0.06] for an IQR increase of

12.6 μ g/m³). In those with a history of asthma, PEF decreased significantly with an increase in the indoor concentration of O₃ (-22.6 L/min [-41.08, -4.13] for an IQR increase). On the other hand, PEF also decreased significantly with an increase in the indoor concentration of O₃ in those with no history of either (-8.84 L/min [-16.28, -1.40] for an IQR increase). In those with a history of allergies, FEV₁ decreased significantly with an increase in the outdoor concentration of PM_{2.5} (-70.0 mL [-130.1, -9.94] for an IQR increase of 18.4 μ g/m³). In addition, FEV₁ decreased significantly with an increase in the indoor concentration of O₃ in subjects with a history of asthma (-130.3 mL [-243.5, -17.2] for an IQR increase).

These results demonstrate that increases in BC and O_3 concentrations have acute effects on pulmonary function among students on an isolated island without major artificial sources of air pollutants. Subjects with a history of asthma or allergies are considered to be more affected by short-term exposure to air pollutants.

4. Conclusions

These studies demonstrate that increases in $PM_{2.5}$ concentrations have short-term effects on asthma attacks and pulmonary function. There were varying degrees of associations between $PM_{2.5}$ concentrations and asthma attacks in relation to age groups and season. It is suggested that acidic chemical constituents, such as WSOC and H⁺, in ambient $PM_{2.5}$ may have a stronger effect of exacerbating asthma in patients. In addition, subjects with asthma or allergic diseases are considered to be more susceptible to air pollution. Further studies with more subjects and longer periods will be necessary to obtain a more detailed evaluation of the health effects of air pollutants, including chemical constituents in $PM_{2.5}$.

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Ethics approval

The protocols of these studies were approval by the Ethics Committee of Hyogo College of Medicine (approval numbers: 1685 and 1474).

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