



Interactive effects of specific fine particulate matter compositions and airborne pollen on frequency of clinic visits for pollinosis in Fukuoka, Japan

Arthit Phosri^a, Kayo Ueda^{a,*}, Saira Tasmin^a, Reiko Kishikawa^b, Masahiko Hayashi^c,
Keiichiro Hara^c, Yamato Uehara^a, Vera Ling Hui Phung^a, Shusuke Yasukouchi^a, Shoko Konishi^{d,e},
Akiko Honda^a, Hirohisa Takano^a

^a Department of Environmental Engineering, Graduate School of Engineering, Kyoto University, Kyoto, Japan

^b The National Hospital Organization (NHO) Fukuoka Hospital, Fukuoka, Japan

^c Department of Earth System Science, Fukuoka University, Fukuoka, Japan

^d Department of Human Ecology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

^e Department of Anthropology, University of Washington, Seattle, USA

ARTICLE INFO

Keywords:

Air pollution
Allergic disease
Particulate matter composition
Pollen
Pollinosis

ABSTRACT

Background: Previous studies have revealed the interactive effects of airborne pollen and particulate matter on the daily consultations for pollinosis, but it is uncertain which compositions are responsible. This study aimed to investigate the interactive effects of specific PM_{2.5} compositions and airborne pollen on the daily number of clinic visits for pollinosis in Fukuoka.

Methods: We obtained daily data on pollen concentrations, PM_{2.5} compositions, PM_{2.5} mass, gaseous pollutants (SO₂, NO₂, CO, and O₃), and weather variables monitored in Fukuoka between February and April, 2002–2012. In total, 73,995 clinic visits for pollinosis were made at 10 clinics in Fukuoka Prefecture during the study period. A time-stratified case-crossover design was applied to examine the interactive effects. The concentrations of PM_{2.5} and its compositions were stratified into low (< 15th percentile), moderate (15th–85th percentile), and high (> 85th percentile) levels, and the association between airborne pollen and daily clinic visits for pollinosis was analyzed within each level.

Results: We found a significant interaction between specific PM_{2.5} compositions and airborne pollen. Specifically, the odds ratio of daily clinic visits for pollinosis per interquartile increase in pollen concentration (39.8 grains/cm³) at the average cumulative lag of 0 and 2 days during high levels of non-sea-salt Ca²⁺ was 1.446 (95% CI: 1.323–1.581), compared to 1.075 (95% CI: 1.067–1.083) when only moderate levels were observed. This result remained significant when other air pollutants were incorporated into the model and was fairly persistent even when different percentile cut-off points were used. A similar interaction was found when we stratified the data according to non-sea-salt SO₄²⁻ levels. This finding differed from estimates made according to PM_{2.5} and NO₃⁻ levels, which predicted that the effects of pollen were strongest in the lower levels.

Conclusions: Associations between airborne pollen and daily clinic visits for pollinosis could be enhanced by high levels of specific PM_{2.5} compositions, especially non-sea-salt Ca²⁺.

1. Introduction

A number of epidemiological studies have found the significant increase in the prevalence of allergic diseases worldwide, especially in developed countries (Burney, 1993). A previous study noted that the prevalences of allergic rhinitis and hay fever during 1991 in Switzerland were 13.5% and 11.6%, respectively (Wüthrich et al., 1995).

Similarly, a study that targeted schoolchildren in Taichung, central Taiwan showed a dramatic increase in the prevalence of allergic rhinitis, from 5.1% in 1987 to 27.6% in 2002 (Liao et al., 2009). Exposure to airborne pollen is an important co-factor responsible for the increased incidence of allergic diseases, especially pollinosis (Wüthrich, 1989). Dispersion of pollen is often affected by climate change, where pollen counts and pollen exposure are likely to change

Abbreviations: PM_{2.5}, particulate matter with aerodynamic diameters less than 2.5 μm; NO₃⁻, nitrate; nss-SO₄²⁻, non-sea-salt sulfate; nss-Ca²⁺, non-sea-salt calcium; SO₂, sulfur dioxide; NO₂, nitrogen dioxide; CO, carbon monoxide; O₃, ozone; CI, confidence interval; ICD, International Classification of Diseases; ADS, Asian dust storm

* Corresponding author.

E-mail address: uedak@health.env.kyoto-u.ac.jp (K. Ueda).

<http://dx.doi.org/10.1016/j.envres.2017.04.008>

Received 11 January 2017; Received in revised form 15 March 2017; Accepted 6 April 2017
0013-9351/ © 2017 Elsevier Inc. All rights reserved.

every year (Bajin et al., 2013; D'Amato et al., 2007; Okamoto et al., 2009; Shea et al., 2008). Pollen typically persists in the atmosphere for longer than 10 weeks after the pollen season and travel distances of over 100 km (Okamoto et al., 2009). A number of studies have recently anticipated that global climate trends to gradually change (Emberlin, 1994; McMichael et al., 2006) and facilitates the spreading of pollen (Beggs, 2004). Thus, the number of patients with pollinosis symptom is possible to increase in the future, which results in people becoming more sensitized to airborne allergen and developing more allergic symptoms (Bajin et al., 2013).

Pollen granules from Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtusa*) are considered the major airborne allergens causing serious pollinosis in Japan (Okuda, 2003). Severity of pollinosis increases during the pollen season, which typically spans from February to May each year, and decreases during the off-pollen season (Okamoto et al., 2009). A recent study revealed that the prevalence of pollinosis in Japan increased by approximately 9% over 10 years from 1998 to 2008 (Nakae and Baba, 2010; Saito, 2014), with considerable differences according to age group and degree of urbanization (Kaneko et al., 2005). Increases in the prevalence of pollinosis in Japan may be due in part to the increased exposure to Japanese cedar antigens (i.e., Cry j 1 and Cry j 2) and the cypress antigen, which are responsible for promoting pollinosis symptoms. Thus, pollinosis caused by airborne pollen should also take into account the amount of allergen present in the pollen (Kuribayashi et al., 2014). The quantities of Cry j 1, a major protein antigen in Japanese cedar pollen, in Japan vary throughout spring which ranged from 0.38 to 10.23 picograms per pollen grain (Saito et al., 2003). Its molecular weight is about 41 kDa and 44 kDa (Wang et al., 2012a). One previous study reported that approximately 70% of patients who are allergic to Japanese cedar are also sensitive to Japanese cypress (Ito et al., 1997). As pollen season for Japanese cypress starts later than that for Japanese cedar, pollinosis caused by Japanese cedar might be aggravated or prolonged by Japanese cypress (Kishikawa et al., 2009). Given the occurrence and potential severity of pollinosis in Japan, annual economic losses due to pollinosis increase are estimated to be 286 billion JPY (Yamamoto et al., 2010).

Sufficient evidence is available to demonstrate that the prevalence of allergic diseases has increased during periods when concentrations of atmospheric pollutants such as oxides of nitrogen, ozone, sulfur dioxide, and particulate matter, are high (Wüthrich, 1989). The Asian Dust Storm (ADS) containing small particulate matter is another potential contributor to increase the prevalence of pollinosis (Wang et al., 2012b; Yamada et al., 2014). This prevalence is particularly evident in industrial areas with high levels of organic pollutants, as well as along main roads with high levels of traffic-related air pollutants (Behrendt et al., 1992; Ishizaki et al., 1987; Wyler et al., 2000). The morphologic structure of pollen might be modulated by airborne particles, which can increase the release of allergenic contents from pollen grains (Behrendt et al., 1997; D'Amato et al., 2007). Gaseous pollutants, such as NO₂, SO₂, O₃, and CO, are also able to modify allergenic proteins in the pollen grain wall which may increase the potential of airborne pollen to exacerbate respiratory allergic diseases in susceptible subjects (Chakra et al., 2010; Ruffin et al., 1985; Wyler et al., 2000). This finding has been supported by an earlier epidemiological study that found that fine particulate matter (PM_{2.5}) enhanced the association between airborne pollen and daily medical consultations for pollinosis in Tokyo, Japan (Konishi et al., 2014). Similarly, the correlation between the number of patients with respiratory allergic diseases and air pollution increased significantly during the *Ambrosia* pollen season in Hungary, supporting the notion that the interaction between air pollution and airborne pollen influences human allergic diseases (Makra et al., 2014).

Although a previous study reported a significant interaction between particulate matter and airborne pollen that influences the number of daily clinic visits for pollinosis (Konishi et al., 2014), the

compositions of particulate matter responsible for this increase remain unclear; in other words, it is unclear whether clinic visits for pollinosis are increased during times when high concentrations of specific PM_{2.5} compositions are observed. To date, no study has examined the interactive effects of specific PM_{2.5} compositions and airborne pollen on respiratory allergic diseases. The present study aimed to estimate whether there is any potential interaction between airborne pollen and the specific compositions of fine particulate matter (PM_{2.5}) on the daily number of clinic visits for pollinosis in Fukuoka, Japan.

2. Methods

The present study was conducted in Fukuoka Prefecture, which is the most populous area of Kyushu, the south-western island of Japan. In 2010, Fukuoka was home to approximately 5.1 million citizens (Ministry of Internal Affairs and Communications, 2015). As Fukuoka is influenced by trans-boundary air pollution, exposure to air pollution is expected to be high (Yoshino et al., 2016). During the spring (February through May), Asian dust containing fine PM and other components is typically carried to Fukuoka by wind from the desert areas of Northern China, Mongolia, and Kazakhstan (Yamada et al., 2014; Zhou et al., 1996). The climate in Fukuoka is moderate, with an annual average temperature of 16.3 °C and average humidity of 70%.

2.1. Clinic visit data

We obtained daily number of patients who were suffering from pollinosis at 10 private otolaryngology and ophthalmology clinics in Fukuoka Prefecture from February 1st through April 30th, 2002–2012. The private clinics located around Fukuoka Prefecture were recruited and one clinic per each ward was selected for participating in this study. Each clinic was not far away from the pollen monitoring station. Hence, the representativeness of private clinics participated in the study were considered to a certain extent although we have no data about socio-economic status for each ward. Data from clinic visits combined those from the first visit and revisits due to pollinosis, which is diagnosed by general practitioners in the clinics using the same criteria throughout the study area. Specific IgE tests were also conducted to differentiate the pollinosis symptoms due to Japanese cedar and Japanese cypress. Pollinosis cases were classified according to the International Classification of Disease, 10th revision (ICD-10), as J30.1. Ethical approval for this study was provided by the Ethics Committee of the Graduate School of Engineering, Kyoto University.

2.2. Pollen data

Daily pollen concentrations of both *Cryptomeria japonica* (Japanese cedar) and *Chamaecyparis obtusa* (Japanese cypress) were obtained from the pollen monitoring station located at the National Hospital Organization (NHO) Fukuoka Hospital. These two pollen species are considered the most important airborne allergens causing pollinosis in Japan (Okamoto et al., 2009). Study patients, who all live and commute within Fukuoka Prefecture, were assigned by daily pollen concentrations representing their daily exposure levels. Pollen density was measured by a gravitational method used widely in Japan that employs a Durham sampler. In this method, pollen grains adhere to vaseline-coated glass slides, which are fixed inside the Durham sampler (Kishikawa et al., 2009). Pollen counts are then standardized and expressed as the number of pollen grains per square centimeter (grains/cm²) on the glass slide. A previous study found that numbers of airborne pollen measured by the Durham sampler at the monitoring station correlated very well with those determined by the volumetric method using a Burkard sampler ($r < 0.923$; P -value < 0.001), the latter of which is typically used in Western countries (Sasaki et al., 2009). The number of pollen grains on the vaseline-coated glass slide was daily determined except for Sunday. Readings for Saturday and

Sunday were thus calculated as the average of the 2-day concentration.

2.3. Environmental data

Daily PM_{2.5} composition data (μg/m³), including non-sea-salt sulfate (nss-SO₄²⁻), non-sea-salt calcium (nss-Ca²⁺), and nitrate (NO₃⁻), were obtained from a monitoring station at Fukuoka University. Size segregated aerosol sampling was conducted daily using a 2-stage filter holder on the roof of the university building. A polycarbonate membrane filter (K800A047A, Advantec; pore size 8.0 μm, 47 mm diameter) and polytetrafluoroethylene (PTFE) membrane filter (T050A047A, Advantec; pore size 0.5 μm, 47 mm diameter) were used for coarse and fine particulate matter sampling, respectively. Filter holders were kept in the weather shield 1.3 m above the roof floor. After sampling, each filter was moved immediately into a polypropylene 15 mL centrifuge vial with an airtight cap in order to prevent contamination during sample storage. Sample vials with filters were packed in polyethylene bags and kept at approximately -25 °C in a freezer until analysis. Blank samples were also taken (2–3 times per month). To determine water-soluble aerosol constituents, aerosol samples were analyzed using ion chromatography (DX-120; Dionex Corp.) following extraction in 14 mL of ultra-pure water. Analytical conditions and procedures followed those described by Hara et al. (2004). Concentrations of sea-salt (ss-) and non-sea-salt (nss-) species in the aerosols were calculated from measured Na⁺ concentrations using bulk seawater ratios (Wilson, 1975).

Hourly PM_{2.5} mass (μg/m³) and other gaseous pollutants including nitrogen dioxide (NO₂; ppbv), sulfur dioxide (SO₂; ppbv), ozone (O₃; ppbv), and carbon monoxide (CO; ppmv) during the study period were provided by the National Institute for Environmental Studies (NIES). Daily average PM_{2.5} mass and gaseous pollutants were calculated using daily 24-h mean values from all available monitoring stations within Fukuoka Prefecture. This calculation excluded days with more than 4 h of missing values. Gaseous pollutants obtained in this study were used to determine the presence of any confounding effects when investigating the interactive effects of specific PM_{2.5} compositions and airborne pollen on the daily number of clinic visits for pollinosis. Data on meteorological variables, including daily average temperature (°C) and relative humidity (%), were obtained from the Japan Meteorological Agency. Fig. 1 displays the location of private clinics, the monitoring station for specific PM_{2.5} compositions, monitoring station for airborne pollen, and monitoring stations for air quality in Fukuoka Prefecture.

2.4. Statistical analysis

A time-stratified case-crossover design was applied to examine the potential interactive effects of specific PM_{2.5} compositions and airborne pollen on the daily number of clinic visits for pollinosis. This statistical approach is an alternative to Poisson time-series regression model for examining transient changes in risk of a rare acute disease (Mackay, 1991). Since the case-crossover design has been developed, it has widely adopted to estimate the association between health effects of interest and air pollution (Chang et al., 2005; Levy et al., 2001; Ueda et al., 2016). The case-crossover approach takes into account comparisons between case period and control period. Each case serves as its own control that is obtained from the same exposure group but during two different periods of time (i.e., before or after the outcome of interest). To select a time-series reference for the present study, exposure to airborne pollen and specific PM_{2.5} compositions at the date of clinic visits for pollinosis (case periods) were compared with that during the same day of the week within the same month of the same year (control periods). This control selection thereby automatically adjusts for day of week, long-term trends, and seasonal effects.

To examine the interaction between PM_{2.5}/its specific compositions and airborne pollen on pollinosis, PM_{2.5} mass, NO₃⁻, nss-SO₄²⁻, and nss-Ca²⁺ were grouped into three levels: low (< 15th percentile), moderate

(15–85th percentile), and high (> 85th percentile). Associations between airborne pollen and the daily numbers of clinic visits for pollinosis were analyzed within each level by fitting a conditional logistic regression model. Results were expressed as an odds ratio and 95% confidence interval per interquartile range increase in daily pollen concentration. As the cut-off values of PM_{2.5} and its compositions were arbitrarily selected, a sensitivity analysis of the effect estimate was then performed using different percentile cut-off points (i.e., 80th and 20th, 75th and 25th, 70th and 30th, and 65th and 35th). We also tested for a statistical significance of the difference between effect estimates of high versus moderate levels of PM_{2.5} and its specific compositions by calculating the 95% confidence interval (CI) as shown below:

$$Q_1 - Q_2 \pm 1.96\sqrt{(SE_1)^2 + (SE_2)^2}, \quad (1)$$

wherein Q₁ and Q₂ are estimates of two categories (high and moderate levels of PM_{2.5} and its specific compositions), and SE₁ and SE₂ are their respective standard errors (Zeka et al., 2006). The P-value for the difference is then calculated using the method applied by Altman and Bland (2011).

The delayed effects of pollen were also examined by analyzing the single-day lag effect up to lag 2, and cumulative lag effect from the current day up to the previous 2 days (lag 02). Based on the preliminary analysis, the effect of airborne pollen on pollinosis remained positive for some time (up to 2 weeks), but its effect was positively persisted up to lag 2 after considering the interactive effects of airborne pollen and PM_{2.5} compositions (data not shown). Thus, we examined the moving average over lag 0 to lag 2 as a core model. Non-stratified effects of pollen were also examined for comparison. Other gaseous pollutants were also simultaneously incorporated into the model to determine the robustness of the effect estimate. Daily mean temperature and relative humidity were linearly adjusted for in the model. All statistical analyses were performed using STATA software (14.0th version).

3. Results

We obtained a total of 73,995 clinic visits for pollinosis, noting a daily average of 96 cases and a maximum of 506 cases per day during the study period. Dispersion of Japanese cedar pollen generally reaches a maximum concentration between the end of February and the beginning of March, and is followed by the dispersion of Japanese cypress pollen, for which the maximum concentration is observed between late March and early April. These dispersions coincided with the peak of clinic visits for pollinosis, which was between the end of February and the end of March (Fig. 2). The distribution of specific PM_{2.5} compositions, PM_{2.5} mass, gaseous pollutants (SO₂, NO₂, CO, and O₃), daily number of clinic visits for pollinosis, and weather variables throughout the study period are shown in Table 1. Standard deviation of pollen concentration across the study period was greater than the average, indicating that fluctuations in daily pollen concentrations are quite variable, ranging between 0 and 968 grains/cm² (Table 1). Daily average nss-Ca²⁺ concentrations were relatively low when compared to those of nss-SO₄²⁻ and NO₃⁻.

When PM_{2.5} and its compositions were stratified using the 85th and 15th percentile cut-off points, the daily numbers of clinic visits for pollinosis during low, moderate, and high levels of PM_{2.5} were 97.8, 93.9, and 95.9, respectively. For NO₃⁻, there were 62.0, 81.2, and 103.3 cases of clinic visits for pollinosis per day during low, moderate, and high levels, respectively. For nss-SO₄²⁻, there were 82.5, 78.9, and 92.1 cases per day for low, moderate, and high levels, respectively. During low, moderate, and high levels of nss-Ca²⁺, the numbers of clinic visits for pollinosis were 72.3, 79.3, and 105.6 cases per day, respectively. PM_{2.5} was highly correlated with nss-SO₄²⁻ (r = 0.72; P-value < 0.01), and was also positively correlated with NO₃⁻, nss-Ca²⁺, SO₂, NO₂, CO, and temperature (Table 2).

The odds ratios of daily clinic visits for pollinosis per interquartile

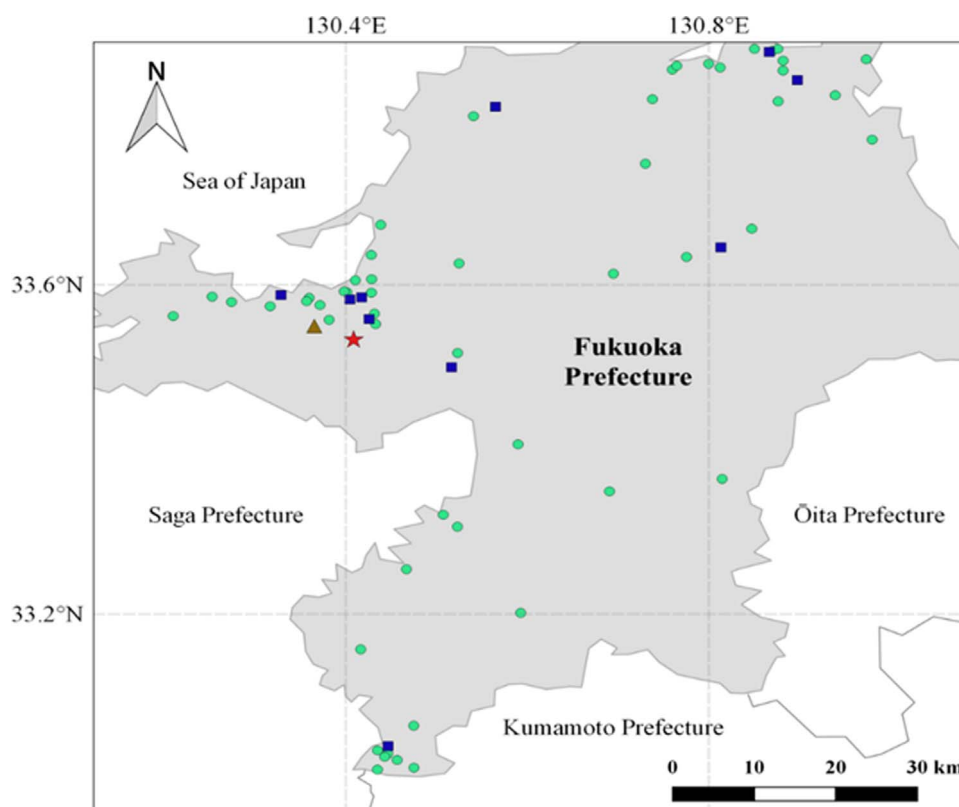


Fig. 1. Map of the study area. The location of private clinics are denoted by rectangles; monitoring station for airborne pollen is denoted by star; monitoring station for specific $PM_{2.5}$ compositions is denoted by triangle; air quality monitoring stations are denoted by circles.

increase (21.5 grains/cm²) in pollen concentration were statistically significant for lag terms up to lag 2, depending upon the level of $PM_{2.5}$ and its specific compositions (Table 3). When $PM_{2.5}$ was stratified into different levels, the pollen effect was significantly higher at moderate levels relative to high levels at lag 0, 1, and 2, as indicated by the *P*-value for the difference between the two levels. At high levels of NO_3^- , the odds ratio of daily clinic visits for pollinosis was significantly strongest for lag 1 and 2. When the effect of pollen was stratified according to $nss-SO_4^{2-}$ level, the odds ratio was significantly larger at moderate levels relative to high levels at lags 0 and 2. Moreover, the estimated effect of pollen was significantly stronger at lag 0 in the high levels of $nss-Ca^{2+}$ when compared to moderate levels, as indicated by the *P*-value for the difference between the two strata (Table 3).

The cumulative effects of pollen during high levels of $PM_{2.5}$ were

lower than those observed during moderate and low levels. This result persisted even after adjusting for other air pollutants (Table 4). This estimated effect was examined per interquartile range increase (39.8 grains/cm²) in pollen concentration on the average of current day up to previous 2 days before clinic visits (the average of lag 0 to lag 2). The association between airborne pollen and daily clinic visits for pollinosis during high levels of NO_3^- was largest and remained stable after inclusion of other air pollutants. The cumulative effects of pollen were also strongest at high levels of $nss-SO_4^{2-}$, and lost significance when SO_2 was incorporated into the model. Similarly, the magnitude of the cumulative effect of pollen was strongest during high levels of $nss-Ca^{2+}$, and lost significance when O_3 was included into the model (Table 4).

When we used different percentile cut-off points for $PM_{2.5}$ and its

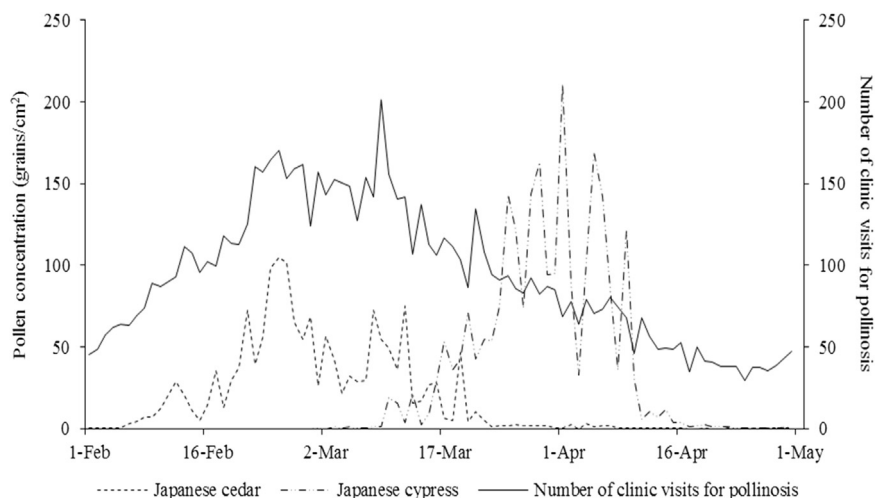


Fig. 2. Daily pollen concentrations and number of clinic visits for pollinosis during February through April, 2012. Mean values throughout the study period are shown.

Table 1

Summary statistics for daily pollen concentrations, number of clinic visits for pollinosis, air pollutant concentrations, and weather variables during February through April, 2002–2012.

Parameters	Days (n)	Mean	SD	Min	P15	P25	Median	P75	P85	Max
Pollen concentration (grains/cm ²)	982	39.17	99.94	0.00	0.00	0.00	2.50	21.50	63.00	967.50
Number of clinic visits for pollinosis	772	95.85	59.65	8.00	42.00	52.00	83.00	123.00	153.00	506.00
Air pollutants										
PM _{2.5} (μg/m ³)	949	22.15	11.67	3.38	12.10	13.97	19.59	27.10	32.70	94.79
NO ₃ ⁻ (μg/m ³)	501	1.11	1.14	0.00	0.30	0.40	0.74	1.27	2.08	7.75
nss-SO ₄ ²⁻ (μg/m ³)	502	5.35	4.22	0.03	1.95	2.54	4.05	7.10	9.32	28.92
nss-Ca ²⁺ (μg/m ³)	486	0.07	0.08	0.00	0.02	0.03	0.05	0.09	0.12	1.21
SO ₂ (ppbv)	982	3.96	1.39	1.42	2.56	2.93	3.75	4.80	5.35	10.70
NO ₂ (ppbv)	982	19.67	6.34	6.52	13.00	14.81	19.00	23.76	26.90	46.33
CO (ppmv)	982	0.63	0.15	0.33	0.49	0.52	0.60	0.71	0.79	1.37
O ₃ (ppbv)	982	33.08	10.92	3.87	21.50	25.19	33.37	39.95	44.59	70.17
Weather variables										
Temperature (°C)	982	11.45	4.29	-0.10	6.70	8.30	11.20	14.50	16.10	24.90
Relative humidity (%)	982	60.72	12.42	27.00	48.00	51.00	59.00	69.00	75.00	94.00

SD: standard deviation; P15: 15th percentile; P25: 25th percentile; P75: 75th percentile; P85: 85th percentile.

PM_{2.5}: fine particulate matter; NO₃⁻: nitrate; nss-SO₄²⁻: non-sea-salt sulfate; nss-Ca²⁺: non-sea-salt calcium.

ppbv: parts per billion by volume; ppmv: parts per million by volume.

Pollen counts included those for both Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtusa*).

specific compositions, the estimated cumulative effect of pollen was primarily stronger during high levels of nss-SO₄²⁻ and nss-Ca²⁺ relative to that during moderate and low levels. Similarly, the effect estimate stratified by NO₃⁻ concentration was strongest in the upper level of the 85th percentile cut-off point. However, the cumulative effects of pollen stratified according to PM_{2.5} concentration were higher in the lower stratum of the 20th, 25th, and 30th percentiles (Table 5).

4. Discussion

In this study, we found that specific PM_{2.5} compositions, such as nss-Ca²⁺, significantly enhanced the association between airborne pollen and daily clinic visits for pollinosis in Fukuoka. The cumulative effect of pollen (average of lag 0–2) was significantly stronger during high levels of nss-Ca²⁺ compared to that observed during moderate and low levels (*P*-value < 0.01). This interaction remained significant after adjusting for other air pollutants (Table 4) and persisted after examining the effect sensitivity using alternative percentile cut-off points. A similar result was also observed in the estimates made according to nss-SO₄²⁻ levels, but was less robust than that of nss-Ca²⁺ as indicated by *P*-value for the differences between high and moderate levels of each composition (Table 5). The cumulative effect of pollen was also strongest during the high levels of NO₃⁻ at particular percentile cut-off points. This finding differed from the estimated effect as stratified by PM_{2.5} concentration, which revealed stronger pollen effects in the lower stratum (Table 5).

A previous study found that exposure to PM_{2.5} increased hospital admissions for asthma and allergic rhinitis with asthma among children

in Turkey with odds ratios of 1.15 (95% CI: 0.99–1.34) and 1.21 (95% CI: 1.10–1.33), respectively (Tecer et al., 2008). However, this association was not observed among children in the United Kingdom, where hospital admissions for asthma were not significantly increased by PM_{2.5} (Anderson et al., 2001). These findings suggest that the effect estimate of PM_{2.5} is complex and potentially varies according to absolute levels of PM_{2.5}, as well as its sources and compositions (Alves et al., 2010; Bell, 2012). A recent study revealed that an interquartile range increase in calcium (Ca²⁺) concentration (0.03 μg/m³) at lag1 was significantly associated with hospital admissions for total respiratory diseases with a percent increase of 4.31% (95% CI: 2.61–6.03%) in the United States (Bell et al., 2014). Similarly, sulfate (SO₄²⁻), nitrate (NO₃⁻), elemental carbon (EC), and organic carbon (OC) are also associated with several respiratory diseases, including pneumonia, bronchitis, and asthma (Ostro et al., 2009). However, the plausible biological mechanisms for these associations have not fully provided. A recent study explained that composition of particulate matter itself is unlikely to be toxic but could be a carrier of bioactive substances to influence health effects (Anderson et al., 2001). This finding is consistent with that of the current study, which found that the association between airborne pollen and pollinosis could be enhanced by high levels of nss-Ca²⁺.

In the current study, we found that the number of daily clinic visits for pollinosis was higher during the pollen season (February through May) (Fig. 2) in places heavily affected by the Asian Dust Storm (ADS), which contains PM_{2.5}, PM_{2.5–10}, and PM₁₀ (Chen et al., 2004; Mimura et al., 2014; Tsai and Chen, 2006). Therefore, dust particles from ADS are likely to aggravate pollinosis symptoms (Mimura et al., 2014; Ogi

Table 2

Spearman correlation coefficients for daily air pollutant concentrations, airborne pollen, and weather variables.

	Pollen	PM _{2.5}	NO ₃ ⁻	nss-SO ₄ ²⁻	nss-Ca ²⁺	SO ₂	NO ₂	CO	O ₃	Temperature
PM _{2.5}	0.127 ⁺									
NO ₃ ⁻	0.110 ⁺	0.373 ⁺								
nss-SO ₄ ²⁻	0.134 ⁺	0.723 ⁺	0.418 ⁺							
nss-Ca ²⁺	-0.006	0.204 ⁺	0.125 ⁺	0.238 ⁺						
SO ₂	0.158 ⁺	0.554 ⁺	0.166 ⁺	0.439 ⁺	0.068					
NO ₂	0.138 ⁺	0.392 ⁺	0.279 ⁺	0.207 ⁺	-0.041	0.635 ⁺				
CO	0.070 ⁺	0.472 ⁺	0.365 ⁺	0.298 ⁺	-0.004	0.600 ⁺	0.833 ⁺			
O ₃	0.027	0.063	-0.151 ⁺	0.180 ⁺	0.090 ⁺	-0.123 ⁺	-0.645 ⁺	-0.540 ⁺		
Temperature	0.083 ⁺	0.222 ⁺	-0.296 ⁺	0.203 ⁺	-0.007	0.223 ⁺	0.062	-0.018	0.288 ⁺	
Humidity	-0.062	-0.042	0.100 ⁺	-0.016	-0.170 ⁺	-0.293 ⁺	0.136 ⁺	0.171 ⁺	-0.395 ⁺	0.120 ⁺

PM_{2.5}: fine particulate matter; NO₃⁻: nitrate; nss-SO₄²⁻: non-sea-salt sulfate; nss-Ca²⁺: non-sea-salt calcium⁺ *P*-value < 0.01.* *P*-value < 0.05.

Table 3

Odds ratio (95% CI) for single-day lag of daily clinic visits for pollinosis per interquartile increase in pollen concentration at each level of PM_{2.5} and its specific compositions as defined by 85th and 15th percentile cut-off points.

Lag terms of airborne pollen ^a	Low (L)	Moderate (M)	High (H)	P-value ^b		Non-stratified model
				H vs. M	L vs. M	
By PM _{2.5} level						
0	0.992 (0.978–1.006)	1.029 (1.027–1.031)	1.001 (0.996–1.006)	< 0.01	< 0.01	1.021 (1.019–1.023)
1	1.019 (1.003–1.037)	1.044 (1.041–1.047)	1.025 (1.019–1.031)	< 0.01	< 0.01	1.034 (1.032–1.036)
2	1.033 (1.018–1.049)	1.036 (1.034–1.038)	1.018 (1.011–1.026)	< 0.01	0.78	1.031 (1.029–1.033)
By NO ₃ [−] level						
0	1.012 (1.007–1.018)	1.016 (1.013–1.019)	0.951 (0.936–0.966)	< 0.01	0.30	1.018 (1.016–1.020)
1	1.031 (1.027–1.036)	1.024 (1.021–1.027)	1.093 (1.066–1.120)	< 0.01	< 0.01	1.024 (1.022–1.026)
2	1.023 (1.018–1.029)	1.018 (1.015–1.021)	1.117 (1.091–1.144)	< 0.01	0.10	1.028 (1.026–1.030)
By nss-SO ₄ ^{2−} level						
0	1.015 (1.008–1.023)	1.018 (1.015–1.021)	0.984 (0.976–0.992)	< 0.01	0.56	1.018 (1.016–1.020)
1	1.031 (1.020–1.042)	1.032 (1.029–1.035)	1.023 (1.010–1.036)	0.15	0.82	1.024 (1.022–1.026)
2	1.017 (1.009–1.026)	1.032 (1.029–1.035)	1.009 (1.001–1.017)	< 0.01	< 0.01	1.028 (1.026–1.030)
By nss-Ca ²⁺ level						
0	1.285 (1.184–1.395)	1.019 (1.016–1.022)	1.413 (1.320–1.513)	< 0.01	< 0.01	1.018 (1.016–1.020)
1	1.587 (1.268–1.986)	1.030 (1.026–1.034)	0.974 (0.886–1.070)	0.24	< 0.01	1.025 (1.023–1.027)
2	1.092 (0.954–1.249)	1.028 (1.025–1.031)	1.067 (1.017–1.118)	0.12	0.38	1.027 (1.025–1.029)

^a All models were adjusted for the delayed effects of ambient temperature and relative humidity as an average of lag 0–2.

^b P-value for differences between high vs moderate and low vs moderate levels of PM_{2.5} and its specific compositions.

Table 4

Odds ratio (95% CI) of daily clinic visits for pollinosis per interquartile increase in pollen concentration at each level of PM_{2.5} and its specific compositions at cumulative lag 0–2 as defined by 85th and 15th percentile cut-off points.

Analyzed model ^a	Low (L)	Moderate (M)	High (H)	P-value ^b		Non-stratified model
				H vs. M	L vs. M	
PM _{2.5} only	1.096 (0.995–1.207)	1.102 (1.097–1.107)	1.058 (1.045–1.071)	< 0.01	0.92	1.085 (1.081–1.089)
PM _{2.5} + SO ₂	1.267 (1.120–1.433)	1.103 (1.098–1.108)	1.052 (1.039–1.065)	< 0.01	0.03	1.085 (1.081–1.089)
PM _{2.5} + NO ₂	1.006 (0.904–1.118)	1.100 (1.095–1.105)	1.034 (1.021–1.048)	< 0.01	0.10	1.082 (1.078–1.087)
PM _{2.5} + CO	1.143 (1.010–1.293)	1.101 (1.095–1.107)	1.048 (1.035–1.061)	< 0.01	0.57	1.084 (1.079–1.088)
PM _{2.5} + O ₃	1.244 (1.111–1.394)	1.099 (1.094–1.104)	1.038 (1.024–1.052)	< 0.01	0.03	1.058 (1.055–1.061)
NO ₃ ⁻ only	1.066 (1.056–1.077)	1.060 (1.051–1.069)	1.190 (1.132–1.251)	< 0.01	0.36	1.067 (1.062–1.071)
NO ₃ ⁻ + SO ₂	1.071 (1.061–1.081)	1.053 (1.044–1.062)	1.176 (1.118–1.237)	< 0.01	0.01	1.060 (1.055–1.065)
NO ₃ ⁻ + NO ₂	1.071 (1.061–1.082)	1.054 (1.045–1.063)	1.196 (1.137–1.258)	< 0.01	0.02	1.060 (1.056–1.065)
NO ₃ ⁻ + CO	1.069 (1.058–1.079)	1.056 (1.047–1.065)	1.158 (1.100–1.220)	< 0.01	0.08	1.061 (1.056–1.065)
NO ₃ ⁻ + O ₃	1.069 (1.058–1.079)	1.057 (1.048–1.066)	1.230 (1.160–1.304)	< 0.01	0.09	1.052 (1.048–1.056)
nss-SO ₄ ²⁻ only	1.071 (1.054–1.088)	1.081 (1.074–1.088)	1.095 (1.066–1.125)	0.37	0.30	1.067 (1.062–1.071)
nss-SO ₄ ²⁻ + SO ₂	1.039 (1.006–1.073)	1.078 (1.071–1.085)	1.013 (0.970–1.059)	< 0.01	0.03	1.060 (1.055–1.065)
nss-SO ₄ ²⁻ + NO ₂	1.070 (1.048–1.091)	1.075 (1.068–1.082)	1.133 (1.094–1.173)	< 0.01	0.66	1.060 (1.056–1.065)
nss-SO ₄ ²⁻ + CO	1.069 (1.052–1.086)	1.078 (1.070–1.086)	1.086 (1.057–1.117)	0.62	0.34	1.061 (1.056–1.065)
nss-SO ₄ ²⁻ + O ₃	1.012 (0.981–1.043)	1.085 (1.078–1.092)	1.101 (1.071–1.131)	0.32	< 0.01	1.052 (1.048–1.056)
nss-Ca ²⁺ only	1.045 (1.028–1.062)	1.075 (1.067–1.083)	1.446 (1.323–1.581)	< 0.01	< 0.01	1.067 (1.062–1.072)
nss-Ca ²⁺ + SO ₂	1.021 (1.004–1.038)	1.075 (1.067–1.084)	1.602 (1.458–1.760)	< 0.01	< 0.01	1.061 (1.056–1.066)
nss-Ca ²⁺ + NO ₂	0.991 (0.972–1.010)	1.080 (1.071–1.088)	1.315 (1.201–1.440)	< 0.01	< 0.01	1.060 (1.055–1.065)
nss-Ca ²⁺ + CO	1.041 (1.023–1.059)	1.077 (1.068–1.085)	1.452 (1.327–1.590)	< 0.01	< 0.01	1.062 (1.057–1.067)
nss-Ca ²⁺ + O ₃	0.991 (0.971–1.010)	1.080 (1.071–1.088)	0.935 (0.814–1.074)	0.04	< 0.01	1.050 (1.046–1.054)

^a All models were adjusted for the delayed effects of ambient temperature and relative humidity as an average of lag 0–2. Air pollutants were simultaneously incorporated into the model with the same average lag term up to lag 2.

^b P-value for differences between high vs moderate and low vs moderate levels of PM_{2.5} and its specific compositions.

et al., 2014; Yamada et al., 2014). This speculation is consistent with a recent study, which found that pollen effects were augmented in the spring when ADS is presented (Watanabe et al., 2011). Although the typical diameter of pollen is around 29–40 μm (Takahashi et al., 1995), major allergens causing pollinosis (i.e., pollen-free Cry j 1) suspended in the air during the pollen season can attach to particles (Takahashi et al., 1991). Therefore, dust particles from ADS can absorb allergens from pollen grains and cause respiratory allergic symptoms (D'Amato et al., 2007). ADS from desert areas of East Asian continent (i.e., Northern China, Mongolia and Kazakhstan) contains significant amounts of iron (Fe), magnesium (Mg), calcium (Ca), silicon (Si), and aluminum (Al) (Cheng et al., 2005; Matsuyama et al., 2008; Yamaguchi et al., 2012). As such, these components are potentially worsen pollinosis symptoms.

Pollinosis symptoms in Japan are typically caused by two major

allergens of Japanese cedar pollen, Cry j 1 and Cry j 2. While Cry j 1 is localized to the Ubisch body, Cry j 2 is found in the starch granule of pollen. These two allergens are abundant in fine PM, especially below 1.1 μm (PM_{1.1}). Thus, it is possible that PM and airborne pollen can be an interactive effect in threatening pollinosis symptoms (Wang et al., 2008). This speculation can be described by the fact that PM alter the morphologic structure of airborne pollen at the surface and within the protoplasm, such as exocytosis of granular proteinaceous material (Behrendt et al., 1997). This alteration is able to induce the release of allergenic proteins (i.e., Cry j 1 and Cry j 2) from pollen grains and give raise to form submicronic protein particles, which may increase the potential of airborne pollen to exacerbate pollinosis symptoms in especially susceptible subjects (Behrendt et al., 1992). An earlier study showed that the association between airborne pollen and daily con-

Table 5

Odds ratios (95% CI) of daily clinic visits for pollinosis per interquartile increase in pollen concentration at each level of PM_{2.5} and its specific compositions at cumulative lag 0–2 as defined by different percentile cut-off points.

Percentile cut-off point ^a	Low (L)	Moderate (M)	High (H)	P-value ^b	
				H vs. M	L vs. M
Stratified by PM _{2.5}					
15th–85th	1.096 (0.995–1.207)	1.102 (1.097–1.107)	1.058 (1.045–1.071)	< 0.01	0.92
20th–80th	1.246 (1.156–1.343)	1.124 (1.117–1.131)	1.052 (1.040–1.065)	< 0.01	< 0.01
25th–75th	1.277 (1.229–1.326)	1.135 (1.128–1.142)	1.049 (1.038–1.060)	< 0.01	< 0.01
30th–70th	1.164 (1.138–1.191)	1.140 (1.130–1.150)	1.054 (1.043–1.064)	< 0.01	0.09
35th–65th	1.104 (1.089–1.118)	1.121 (1.109–1.133)	1.077 (1.067–1.086)	< 0.01	0.06
Stratified by NO ₃ [−]					
15th–85th	1.066 (1.056–1.077)	1.060 (1.051–1.069)	1.190 (1.132–1.251)	< 0.01	0.36
20th–80th	1.063 (1.054–1.072)	1.044 (1.034–1.054)	1.031 (1.009–1.053)	0.27	< 0.01
25th–75th	1.067 (1.058–1.075)	1.054 (1.039–1.069)	1.053 (1.032–1.074)	0.96	0.12
30th–70th	1.072 (1.064–1.080)	1.062 (1.041–1.083)	1.059 (1.041–1.077)	0.86	0.37
35th–65th	1.069 (1.062–1.076)	1.102 (1.062–1.144)	1.050 (1.036–1.063)	0.01	0.11
Stratified by nss-SO ₄ ^{2−}					
15th–85th	1.071 (1.054–1.088)	1.081 (1.074–1.088)	1.095 (1.066–1.125)	0.37	0.30
20th–80th	1.055 (1.040–1.070)	1.082 (1.074–1.090)	1.092 (1.069–1.115)	0.42	< 0.01
25th–75th	1.052 (1.038–1.067)	1.115 (1.105–1.125)	1.049 (1.032–1.067)	< 0.01	< 0.01
30th–70th	1.054 (1.042–1.066)	1.114 (1.102–1.126)	1.070 (1.055–1.085)	< 0.01	< 0.01
35th–65th	1.061 (1.049–1.072)	1.061 (1.045–1.077)	1.134 (1.119–1.148)	< 0.01	0.99
Stratified by nss-Ca ²⁺					
15th–85th	1.045 (1.028–1.062)	1.075 (1.067–1.083)	1.446 (1.323–1.581)	< 0.01	< 0.01
20th–80th	1.047 (1.030–1.063)	1.065 (1.056–1.074)	1.488 (1.363–1.625)	< 0.01	0.06
25th–75th	1.035 (1.021–1.049)	1.056 (1.046–1.066)	1.032 (0.990–1.077)	0.30	0.02
30th–70th	1.036 (1.022–1.050)	1.064 (1.053–1.075)	1.126 (1.086–1.167)	< 0.01	< 0.01
35th–65th	1.038 (1.027–1.049)	1.062 (1.048–1.076)	1.053 (1.030–1.076)	0.52	0.01

PM_{2.5}: fine particulate matter; NO₃⁻: nitrate; nss-SO₄²⁻: non-sea-salt sulfate; nss-Ca²⁺: non-sea-salt calcium.

^a All models were adjusted for the delayed effects of ambient temperature and relative humidity as an average of lag 0–2.

^b P-value for differences between high vs moderate and low vs moderate levels of PM_{2.5} and its specific compositions.

sultations for pollinosis was stronger during high concentrations of PM_{2.5} with a percent increase of 10.30% (95% CI: 8.48–12.16%) in Tokyo (Konishi et al., 2014). However, the current study did not find similar results; instead, we found that pollen effects were stronger at lower levels of PM_{2.5}. Although the cumulative effects of pollen were stronger during low levels, the estimated effect was also significant during high levels (Table 5). It is unlikely that our results can be caused by statistical approach, because this method has been used recently by another study conducted in Tokyo, with reasonable results. We also did a sensitivity analysis using different percentile cut-off points as well as adjusted for confounding due to meteorological variables, and the results remained the same. One possible explanation of that different result is that we combined the number of first visits and revisits for pollinosis, whereas the study conducted in Tokyo included only the number of first visits, which may have led to different results. Given the present study results, we hypothesize that even low levels of PM_{2.5} might enhance the effects of airborne pollen on pollinosis. Findings from our study and a previous study suggest that effects of PM_{2.5} may also vary by location.

The present study revealed that the association between airborne pollen and pollinosis was stronger during high concentrations of nss-Ca²⁺. This association was more robust than the estimated effect stratified according to nss-SO₄²⁻ and NO₃⁻ concentrations as indicated by the P-value for the difference between high and moderate levels at particular percentile cut-off points of each composition. This result may be explained by the influence of soil particles from Asian dust events, which contain large quantities of nss-Ca²⁺ (Suzuki and Tsunogai, 1988; Tsai and Chen, 2006). Support for this finding comes from a previous study reporting that 60% of allergenic Cry j 1 released from the Ubisch body to the air environment contained a high amount of Ca²⁺ derived from ADS (Wang et al., 2012b). It would follow, therefore, that nss-Ca²⁺ may enhance the effects of airborne pollen on pollinosis.

The delayed effects of pollen were observed because the major allergenic protein causing pollinosis, Cry j 1, is found in the air after a

few days of the peak concentration of intact airborne pollen and is remained in the air for some time (Takahashi et al., 1991). Hence, the concentration of airborne pollen on previous day might be associated with Cry j 1 level on the current day which then leads to the observed delayed effects of airborne pollen.

We noted that the association between airborne pollen and pollinosis can be significantly augmented by PM_{2.5}, even at very low concentrations. However, the estimated effect of PM_{2.5} may differ by location and time depending on its compositions. Our study is the first to show the interactive effect of airborne pollen and specific compositions of PM_{2.5} on pollinosis symptoms. PM_{2.5} carrying its compositions can bind to the pollen surface and induce the release of allergenic contents from pollen grains (Behrendt et al., 1992). Once allergens reach the airway and mucosa, they are taken up by antigen presenting cells such as dendritic cells and macrophages, which present the antigen to T-lymphocytes associated with the production of IgE antibodies. These antibodies then interact with the surface of inflammatory cells (i.e., mast cells) to promote allergic sensitivity, where pollinosis symptoms could occur (Jayasekera et al., 2007).

The present study has several limitations. First, the daily number of clinic visits for pollinosis was available only for 10 clinics in Fukuoka Prefecture, which might affect the estimated effect of pollen. Second, we included the clinic visit data from the first visit and revisit due to pollinosis for the analysis. These data might be a source of bias for the current study. Third, we used the dataset from only one monitoring station to represent personal exposure to PM_{2.5} compositions and airborne pollen for patients living and commuting around Fukuoka Prefecture, which may not accurately reflect as exposure levels. Moreover, there were many daily missing values for PM_{2.5} compositions throughout the study period. Although these limitations may affect the effect estimate, we found a significant interaction between specific PM_{2.5} compositions and airborne pollen that affected pollinosis symptoms. The current study is the first to report the interactive effects of PM_{2.5} compositions and airborne pollen on respiratory allergic symp-

toms using information from daily clinic visits for pollinosis in Fukuoka, Japan. Replication of this study in other locations will help to corroborate our findings.

5. Conclusion

This study found that the interactive effects of PM_{2.5} and airborne pollen on pollinosis symptoms differed from those reported by previous studies. Therefore, the effects of PM_{2.5} may vary according to location and its composition. Our study found that the interactive effects between specific PM_{2.5} compositions (especially nss-Ca²⁺) and airborne pollen increased the daily number of clinic visits for pollinosis in Fukuoka during the pollen seasons of the study period. We surmise that the presence of specific PM_{2.5} compositions and airborne pollen in the air can perform as a joint effect in exacerbating respiratory allergic health outcomes (i.e., pollinosis).

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding source

This study was supported by a grant-in-aid from the Japanese Ministry of the Environment (S12 and 5–1452). The funding agency had no role in the design, data collection, data analysis, and preparation of the manuscript.

Ethical consideration

This study was approved by the ethical committee of the Graduate School of Engineering, Kyoto University. Written informed consent was not required in this study because we used aggregated data and no individual data.

Acknowledgements

This study was supported by a grant-in-aid from the Japanese Ministry of the Environment (S12 and 5–1452). We would like to express our sincere gratitude to otolaryngology and ophthalmology clinics in Fukuoka, as well as Fukuoka University, the National Hospital Organization (NHO) Fukuoka Hospital, the Japan Meteorological Agency, and the National Institute for Environmental Studies for providing the data for this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.envres.2017.04.008](https://doi.org/10.1016/j.envres.2017.04.008).

References

- Altman, D.G., Bland, J.M., 2011. How to obtain the P value from a confidence interval. *BMJ* 343, 1–2. [http://dx.doi.org/10.1136/bmj.d2304](https://doi.org/10.1136/bmj.d2304).
- Alves, C.A., Scotto, M.G., Freitas, M.D.C., 2010. Air pollution and emergency admissions for cardiorespiratory diseases in Lisbon (Portugal). *Quím. Nova* 33, 337–344. [http://dx.doi.org/10.1590/S0100-40422010000200020](https://doi.org/10.1590/S0100-40422010000200020).
- Anderson, H.R., Bremner, S.A., Atkinson, R.W., Harrison, R.M., Walters, S., 2001. Particulate matter and daily mortality and hospital admissions in the west midlands conurbation of the United Kingdom: associations with fine and coarse particles, black smoke and sulphate. *Occup. Environ. Med.* 58, 504–510. [http://dx.doi.org/10.1136/oem.58.8.504](https://doi.org/10.1136/oem.58.8.504).
- Bajin, M.D., Cingi, C., Oghan, F., Gurbuz, M.K., 2013. Global warming and allergy in Asia Minor. *Eur. Arch. Otorhinolaryngol.* 270, 27–31.
- Beggs, P.J., 2004. Impacts of climate change on aeroallergens: past and future. *Clin. Exp. Allergy* 34, 1507–1513. [http://dx.doi.org/10.1111/j.1365-2222.2004.02061.x](https://doi.org/10.1111/j.1365-2222.2004.02061.x).
- Behrendt, H., Becker, W.M., Friedrichs, K.H., Darsow, U., Tomingas, R., 1992. Interaction between Aeroallergens and Airborne Particulate Matter. *Int. Arch. Allergy Immunol.* 99, 425–428.
- Behrendt, H., Becker, W.M., Fritzsche, C., Sliwa-Tomczok, W., Tomczok, J., Friedrichs, K.H., et al., 1997. Air Pollution and Allergy: experimental Studies on Modulation of Allergen Release from Pollen by Air Pollutants. *Int. Arch. Allergy Immunol.* 113, 69–74.
- Bell, M.L., 2012. Assessment of the health impacts of particulate matter characteristics. *Res. Rep. Health Eff. Inst.* 161, 5–38.
- Bell, M.L., Ebisu, K., Leaderer, B.P., Gent, J.F., Lee, H.J., Koutrakis, P., et al., 2014. Associations of PM_{2.5} Constituents and Sources with Hospital Admissions: analysis of Four Counties in Connecticut and Massachusetts (USA) for Persons ≥ 65 Years of Age. *Environ. Health Perspect.* 122, 138–144. [http://dx.doi.org/10.1289/ehp.1306656](https://doi.org/10.1289/ehp.1306656).
- Burney, P.G.J., 1993. Evidence for an increase in atopic disease and possible causes. *Clin. Exp. Allergy* 23, 484–492. [http://dx.doi.org/10.1111/j.1365-2222.1993.tb03235.x](https://doi.org/10.1111/j.1365-2222.1993.tb03235.x).
- Chakra, O.R.A., Lacroix, G., Senechal, H., Thibaudon, M., 2010. Synergy pollen-pollutants and roles of meteorological factors on the pollinosis: evolution of consultations in the Amiens city during the pollen season in 2007. *Rev. Fr. Allergol.* 50, 443–449. [http://dx.doi.org/10.1016/j.reval.2009.11.002](https://doi.org/10.1016/j.reval.2009.11.002).
- Chang, C.C., Tsai, S.S., Ho, S.C., Yang, C.Y., 2005. Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. *Environ. Res.* 98, 114–119. [http://dx.doi.org/10.1016/j.envres.2004.07.005](https://doi.org/10.1016/j.envres.2004.07.005).
- Chen, S.J., Hsieh, L.T., Kao, M.J., Lin, W.Y., Huang, K.L., Lin, C.C., 2004. Characteristics of particles sampled in southern Taiwan during the Asian dust storm periods in 2000 and 2001. *Atmos. Environ.* 38, 5925–5934. [http://dx.doi.org/10.1016/j.atmosenv.2004.07.006](https://doi.org/10.1016/j.atmosenv.2004.07.006).
- Cheng, M.T., Lin, Y.C., Chio, C.P., Wang, C.F., Kuo, C.Y., 2005. Characteristics of aerosols collected in central Taiwan during an Asian dust event in spring 2000. *Chemosphere* 61, 1439–1450. [http://dx.doi.org/10.1016/j.chemosphere.2005.04.120](https://doi.org/10.1016/j.chemosphere.2005.04.120).
- D'Amato, G., Cecchi, L., Bonini, S., Nunes, C., Annesi-Maesano, I., Behrendt, H., et al., 2007. Allergic pollen and pollen allergy in Europe. *Allergy* 62, 976–990. [http://dx.doi.org/10.1111/j.1398-9995.2007.01393.x](https://doi.org/10.1111/j.1398-9995.2007.01393.x).
- Emberlin, J., 1994. The effects of patterns in climate and pollen abundance on allergy. *Allergy* 49, 15–20.
- Hara, K., Osada, K., Kido, M., Hayashi, M., Matsunaga, K., Iwasaka, Y., et al., 2004. Chemistry of sea-salt particles and inorganic halogen species in Antarctic regions: compositional differences between coastal and inland stations. *J. Geophys. Res.* 109, 1–18. [http://dx.doi.org/10.1029/2004JD004713](https://doi.org/10.1029/2004JD004713).
- Ishizaki, T., Koizumi, K., Ikemori, R., Ishiyama, Y., Kushibiki, E., 1987. Studies of prevalence of Japanese cedar pollinosis among the residents in a densely cultivated area. *Ann. Allergy* 58, 265. [http://www.ncbi.nlm.nih.gov/pubmed/3565861](https://pubmed.ncbi.nlm.nih.gov/pubmed/3565861).
- Ito, Y., Takahashi, Y., Fujita, T., Fukuyama, S., 1997. Clinical effects of immunotherapy on Japanese cedar pollinosis in the season of cedar and cypress pollination. *Auris Nasus Larynx* 24, 163–170. [http://dx.doi.org/10.1016/S0385-8146\(96\)00028-4](https://doi.org/10.1016/S0385-8146(96)00028-4).
- Jayasekera, N.P., Toma, T.P., Williams, A., Rajakulasingam, K., 2007. Mechanisms of immunotherapy in allergic rhinitis. *Biomed. Pharmacother.* 61, 29–33. [http://dx.doi.org/10.1016/j.biopha.2006.09.013](https://doi.org/10.1016/j.biopha.2006.09.013).
- Kaneko, Y., Motohashi, Y., Nakamura, H., Endo, T., Eboshida, A., 2005. Increasing prevalence of Japanese cedar pollinosis: a meta-regression analysis. *Int. Arch. Allergy Immunol.* 136, 365–371. [http://dx.doi.org/10.1159/000084256](https://doi.org/10.1159/000084256).
- Kishikawa, R., Sahashi, N., Saitoh, A., Kotoh, E., Shimoda, T., Shoji, S., et al., 2009. Japanese Cedar Airborne Pollen Monitoring by Durham's and Burkard Samplers in Japan—Estimation of the Usefulness of Durham's Sampler on Japanese Cedar Pollinosis. *Glob. Environ. Res.* 13, 55–62.
- Konishi, S., Ng, C.F.S., Stickley, A., Nishihata, S., Shinsugi, C., Ueda, K., et al., 2014. Particulate matter modifies the association between airborne pollen and daily medical consultations for pollinosis in Tokyo. *Sci. Total Environ.* 499, 125–132. [http://dx.doi.org/10.1016/j.scitotenv.2014.08.045](https://doi.org/10.1016/j.scitotenv.2014.08.045).
- Kuribayashi, T., Seita, T., Takada, K., Honjo, T., 2014. Changes in quantity of Cry j1, a major cedar pollinosis allergen, in *Cryptomeria japonica* pollen during spring in Japan. *Food Agric. Immunol.* 25, 267–274.
- Levy, D., Lumley, T., Sheppard, L., Kaufman, J., Checkoway, H., 2001. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology* 12, 186–192. [http://dx.doi.org/10.1097/00001648-200103000-00010](https://doi.org/10.1097/00001648-200103000-00010).
- Liao, P.F., Sun, H.L., Lu, K.H., Lue, K.H., 2009. Prevalence of childhood allergic diseases in central Taiwan over the past 15 years. *Pediatr. Neonatol.* 50, 18–25. [http://dx.doi.org/10.1016/S1875-9572\(09\)60025-5](https://doi.org/10.1016/S1875-9572(09)60025-5).
- Maclure, M., 1991. The Case-Crossover Design: a Method for Studying Transient Effects on the Risk of Acute Events. *Am. J. Epidemiol.* 133, 144–153.
- Makra, L., Matyasovszky, I., Bálint, B., Csépe, Z., 2014. Association of allergic rhinitis or asthma with pollen and chemical pollutants in Szeged, Hungary, 1999–2007. *Int. J. Biometeorol.* 58, 753–768. [http://dx.doi.org/10.1007/s00484-013-0656-9](https://doi.org/10.1007/s00484-013-0656-9).
- Matsuyama, S., Ishii, K., Yamazaki, H., Kikuchi, Y., Kawamura, Y., Oyama, R., et al., 2008. Microbeam analysis of yellow sand dust particles. *X Ray Spectrom.* 37, 151–155. [http://dx.doi.org/10.1002/xrs](https://doi.org/10.1002/xrs).
- McMichael, A.J., Woodruff, R.E., Hales, S., 2006. Climate change and human health: present and future risks. *Lancet* 367, 859–869. [http://dx.doi.org/10.1016/S0140-6736\(06\)68079-3](https://doi.org/10.1016/S0140-6736(06)68079-3).
- Mimura, T., Yamagami, S., Fujishima, H., Noma, H., Kamei, Y., Goto, M., et al., 2014. Sensitization to Asian dust and allergic rhinoconjunctivitis. *Environ. Res.* 132, 220–225. [http://dx.doi.org/10.1016/j.envres.2014.04.014](https://doi.org/10.1016/j.envres.2014.04.014).
- Ministry of Internal Affairs and Communications, 2015. (Ed.). Statistical handbook of Japan 2015. Shinjuku-ku, Tokyo, pp. 191. <http://www.stat.go.jp/english/data/handbook/index.htm>.
- Nakae, K., Baba, K., 2010. Update on epidemiology of pollinosis in Japan: changes over the last 10 years. *Clin. Exp. Allergy Rev.* 10, 2–7. [http://dx.doi.org/10.1111/j.1472-9733.2010.01148.x](https://doi.org/10.1111/j.1472-9733.2010.01148.x).
- Ogi, K., Takabayashi, T., Sakashita, M., Susuki, D., Yamada, T., Manabe, Y., et al., 2014. Effect of Asian sand dust on Japanese cedar pollinosis. *Auris Nasus Larynx* 41, 518–522. [http://dx.doi.org/10.1016/j.anl.2014.05.020](https://doi.org/10.1016/j.anl.2014.05.020).

- Okamoto, Y., Horiguchi, S., Yamamoto, H., Yonekura, S., Hanazawa, T., 2009. Present situation of cedar pollinosis in Japan and its immune responses. *Allergol. Int.* 58, 155–162. <http://dx.doi.org/10.2332/allergolint.08-RAI-0074>.
- Okuda, M., 2003. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann. Allergy Asthma Immunol.* 91, 288–296. [http://dx.doi.org/10.1016/S1081-1206\(10\)63532-6](http://dx.doi.org/10.1016/S1081-1206(10)63532-6).
- Ostro, B., Roth, L., Malig, B., Marty, M., 2009. The effects of fine particle components on respiratory hospital admissions in children. *Environ. Health Perspect.* 117, 475–480. <http://dx.doi.org/10.1289/ehp.11848>.
- Ruffin, J., Liu, M.Y., Sessoms, R., Banerjee, S., Banerjee, U.C., 1985. Effects of certain atmospheric pollutants (SO₂, NO₂ and CO) on the soluble amino acids, molecular weight and antigenicity of some airborne pollen grains. *Cytobios* 46, 119–129.
- Saito, M., Teranishi, H., Taira, H., 2003. Study on the Variation of Cry j 1 Content per Pollen Grain among 420 Clones in 25 Prefectures and Estimating of Heritability on Cry j 1 in Sugi (*Cryptomeria japonica* D. Don). *J. Jpn. For. Soc.* 85, 312–317 (in Japanese).
- Saito, Y., 2014. Japanese cedar pollinosis: discovery, nomenclature, and epidemiological trends. *Proc. Jpn. Acad. Ser. B. Phys. Biol. Sci.* 90, 203–210. <http://dx.doi.org/10.2183/pjab.90.203>.
- Sasaki, K., Okamoto, Y., Yonekura, S., Okawa, T., Horiguchi, S., Chazono, H., et al., 2009. Cedar and cypress pollinosis and allergic rhinitis: quality of life effects of early intervention with leukotriene receptor antagonists. *Int. Arch. Allergy Immunol.* 149, 350–358. <http://dx.doi.org/10.1159/000205581>.
- Shea, K.M., Truckner, R.T., Weber, R.W., Peden, D.B., 2008. Climate change and allergic disease. *J. Allergy Clin. Immunol.* 122, 443–453. <http://dx.doi.org/10.1016/j.jaci.2008.06.032>.
- Suzuki, T., Tsunogai, S., 1988. Origin of calcium in aerosols over the western North Pacific. *J. Atmos. Chem.* 6, 363–374. <http://dx.doi.org/10.1007/BF00051597>.
- Takahashi, Y., Sakaguchi, M., Inouye, S., Miyazawa, H., Imaoka, K., Katagiri, S., 1991. Existence of exine-free airborne allergen particles of Japanese cedar (*Cryptomeria japonica*) pollen. *Allergy* 46, 588–593.
- Takahashi, Y., Sasaki, K., Nakamura, S., Miki-Hirosige, H., Nitta, H., 1995. Aerodynamic size distribution of the particles emitted from the flowers of allergologically important plants. *Grana* 34, 45–49. <http://dx.doi.org/10.1080/00173139509429032>.
- Tecer, L.H., Alagha, O., Karaca, F., Tuncel, G., Eldes, N., 2008. Particulate matter (PM_{2.5}, PM_{10-2.5}, and PM₁₀) and children's hospital admissions for asthma and respiratory diseases: a bidirectional case-crossover study. *J. Toxicol. Environ. Health Part A* 71, 512–520. <http://dx.doi.org/10.1080/15287390801907459>.
- Tsai, Y.I., Chen, C.L., 2006. Characterization of Asian dust storm and non-Asian dust storm PM_{2.5} aerosol in southern Taiwan. *Atmos. Environ.* 40, 4734–4750. <http://dx.doi.org/10.1016/j.atmosenv.2006.04.038>.
- Ueda, K., Yamagami, M., Ikemori, F., Hisatsune, K., Nitta, H., 2016. Associations Between Fine Particulate Matter Components and Daily Mortality in Nagoya, Japan. *J. Epidemiol.* 26, 249–257. <http://dx.doi.org/10.2188/jea.JE20150039>.
- Wang, Q., Kurihara, K., Kiryu, H., Sakamoto, K., Miwa, M., Uchiyama, I., 2008. Daily variation differences between airborne Japanese cedar pollen and its respirable allergen particulate matters during the most severe pollination seasons. *Eurozoru Kenkyu* 23, 120–126.
- Wang, Q., Morita, J., Gong, X., Nakamura, S., Suzuki, M., Lu, S., et al., 2012a. Characterization of the physical form of allergenic cry j 1 in the urban atmosphere and determination of Cry j 1 denaturation by air pollutants. *Asian J. Atmos. Environ.* 6, 33–40.
- Wang, Q., Nakamura, S., Lu, S., Xiu, G., Nakajima, D., Suzuki, M., et al., 2012b. Release behavior of small sized daughter allergens from *Cryptomeria japonica* pollen grains during urban rainfall event. *Aerobiologia* 28, 71–81. <http://dx.doi.org/10.1007/s10453-011-9212-4>.
- Watanabe, M., Igishi, T., Burioka, N., Yamasaki, A., Kurai, J., Takeuchi, H., et al., 2011. Pollen augments the influence of desert dust on symptoms of adult asthma patients. *Allergol. Int.* 60, 517–524. <http://dx.doi.org/10.2332/allergolint.10-OA-0298>.
- Wilson, T.R.S., 1975. Salinity and the major elements of sea water. In: Riley, J.P., Skirrow, G. (Eds.), *Chemical Oceanography* 1. Academic Press, New York, pp. 365–413.
- Wüthrich, B., 1989. Epidemiology of the allergic disease: are they really on the increase? *Int. Arch. Allergy Immunol.* 90, 3–10.
- Wüthrich, B., Schindler, C., Leuenberger, P., Ackermann-Liebrich, U., 1995. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). *Int. Arch. Allergy Immunol.* 106, 149–156.
- Wyler, C., Braun-Fahrlander, C., Künzli, N., Schindler, C., Ackermann-Liebrich, U., Perruchoud, A.P., et al., 2000. Exposure to Motor Vehicle Traffic and Allergic Sensitization. *Epidemiology* 11, 450–456.
- Yamada, T., Saito, H., Fujieda, S., 2014. Present state of Japanese cedar pollinosis: the national affliction. *J. Allergy Clin. Immunol.* 133, 632–639. <http://dx.doi.org/10.1016/j.jaci.2013.11.002>.
- Yamaguchi, N., Ichijo, T., Sakotani, A., Baba, T., Nasu, M., 2012. Global dispersion of bacterial cells on Asian dust. *Sci. Rep.* 2, 1–6. <http://dx.doi.org/10.1038/srep00525>.
- Yamamoto, N., Nishikawa, J., Sakamoto, M., Shimizu, T., Matsuki, H., 2010. Indoor and outdoor concentrations of Japanese cedar pollens and total suspended particulates: a case study at a kindergarten in Japan. *Build. Environ.* 45, 792–797. <http://dx.doi.org/10.1016/j.buildenv.2009.08.002>.
- Yoshino, A., Takami, A., Sato, K., Shimizu, A., Kaneyasu, N., Hatakeyama, S., et al., 2016. Influence of Trans-Boundary Air Pollution on the Urban Atmosphere in Fukuoka, Japan. *Atmosphere* 7, 51. <http://dx.doi.org/10.3390/atmos7040051>.
- Zeka, A., Zanobetti, A., Schwartz, J., 2006. Individual-level modifiers of the effects of particulate matter on daily mortality. *Am. J. Epidemiol.* 163, 849–859. <http://dx.doi.org/10.1093/aje/kwj116>.
- Zhou, M., Okada, K., Qian, F., Wu, P.M., Su, L., Casareto, B.E., et al., 1996. Characteristics of dust-storm particles and their long-range transport from China to Japan - Case studies in April 1993. *Atmos. Res.* 40, 19–31. [http://dx.doi.org/10.1016/0169-8095\(95\)00023-2](http://dx.doi.org/10.1016/0169-8095(95)00023-2).