



Particulate matter modifies the association between airborne pollen and daily medical consultations for pollinosis in Tokyo



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HIGHLIGHTS

- Ambient PM_{2.5} and SPM modify the effect of pollen on daily new cases of pollinosis.
- The cumulative effect of pollen was larger with higher levels of PM_{2.5} and SPM.
- Particulate pollutants may act as an adjuvant to promote pollinosis symptoms.

ARTICLE INFO

Article history:

Received 18 April 2014

Received in revised form 21 July 2014

Accepted 15 August 2014

Available online xxxx

Editor: Lidia Morawska

Keywords:

Air pollution

Allergy

Particulate matter

Pollen

Pollinosis

ABSTRACT

Pollen from Japanese cedar (*sugi*) and cypress (*hinoki*) trees is responsible for the growing prevalence of allergic rhinitis, especially pollinosis in Japan. Previous studies have suggested that air pollutants enhance the allergic response to pollen in susceptible individuals. We conducted a time-stratified case-crossover study to examine the potential modifying effects of PM_{2.5} and suspended particulate matter (SPM) on the association between pollen concentration and daily consultations for pollinosis. A total of 11,713 daily pollinosis cases (International Classification of Diseases, ICD-10, J30.1) from January to May, 2001–2011, were obtained from a clinic in Chiyoda, Tokyo. Daily pollen counts and the daily mean values of air pollutants (PM_{2.5}, SPM, SO₂, NO₂, CO, and O₃) were collected from monitoring stations across Tokyo. The effects of pollen were stratified by the level of PM_{2.5} and SPM to examine the interaction effect of pollen and particulate pollutants. We found a statistically significant interaction between pollen concentration and PM_{2.5}/SPM. On days with a high level of PM_{2.5} (>95th percentile), an interquartile increase in the mean cumulative pollen count (an average of 28 pollen grains per cm² during lag-days 0 to 5) corresponded to a 10.30% (95%CI: 8.48%–12.16%) increase in daily new pollinosis cases, compared to 8.04% (95%CI: 7.28%–8.81%) on days with a moderate level of PM_{2.5} (5th–95th percentile). This interaction persisted when different percentile cut-offs were used and was robust to the inclusion of other air pollutants. A similar interaction pattern was observed between SPM and pollen when a less extreme cut-off for SPM was used to stratify the effect of pollen. Our study showed the acute effect of pollen was greater when the concentration of air particulate pollutant, specifically PM_{2.5} and SPM, was higher. These findings are consistent with the notion that particulate air pollution may act as an adjuvant that promotes allergic disease (i.e. pollinosis).

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1. Introduction

Japanese cedar (*Cryptomeria japonica*) pollen is the most common and potent seasonal allergen causing seasonal allergic rhinitis in Japan

(Okubo et al., 2005). A sharp growth in the number of cases of Japanese cedar pollinosis (hereafter termed pollinosis) during the last two decades has led to it being recently described as a ‘national affliction’ (Yamada et al., 2014). A recent study has documented for instance, how the overall prevalence of pollinosis in Japan rose from 17.4% in 1998 to 26.5% in 2008 (Nakae and Baba, 2010), while other authors have suggested that more than one-third of the population may be currently suffering from pollinosis (Yamada et al., 2014). All age groups are being affected by the occurrence of pollinosis (Okuda, 2003; Ozasa

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et al., 2002), with its associated symptoms of sneezing, rhinorrhea, nasal itching, obstruction, and eye irritation (Tanaka et al., 2012) interfering severely with the daily activities of almost one-third of sufferers during the pollen season (Okuda, 2003) (which usually stretches from February to April each year). Given the extent of its occurrence and the potential severity of its symptoms, pollinosis now constitutes a major public health problem in Japan (Okuda, 2003) with the annual economic losses that result from it estimated to be in excess of 280 billion yen (Yamamoto et al., 2010).

The sharp growth in the prevalence of pollinosis in Japan in recent years may be due to the higher exposure of the population to Japanese cedar pollen antigens, i.e. Cry j 1 and Cry j 2 (Nakae and Baba, 2010; Nakamura et al., 2004), cypress pollen antigens (Ganbo et al., 1995), and to the high cross-antigenicity between these two pollen species. This was highlighted in an earlier Japanese study which showed that 69% of patients who tested positive for cedar antigens were also positive for cypress antigens (Ganbo et al., 1995). The precursor for the current situation lies in the period that followed in the wake of World War II when Japanese cedar and cypress trees were cultivated as a source of cheap building material. Cheaper wood imports from the mid-1960s onward however, meant that most foresters eventually abandoned the industry, leaving these trees – which cover 19% of the land area of Japan – to continue growing unattended (Yamada et al., 2014). This situation may have been further exacerbated by the effect of climate change which has been linked to a possible increase in the amount of pollen aeroallergen (Beggs, 2004). In Japan specifically, the average temperature has increased by 1.15 °C in the past century (Yamada et al., 2014), with researchers linking higher temperatures to the earlier occurrence of the pollen season (Teranashi et al., 2006).

Despite some evidence that cedar pollen counts in Japan were significantly higher in the period 1995 to 2013 compared with 1965 to 1994 (Yamada et al., 2014), and that there is a correlation between regional pollen counts and the occurrence of cedar pollinosis (Okuda, 2003), it is also possible that other factors may be affecting the pollen-pollinosis relation. In particular, an early study showed that in areas in Japan where pollen counts were nearly identical, the incidence of pollinosis was higher among residents living along main roads (Ishizaki et al., 1987). Together with this, the fact that more recent research has highlighted that the pollen sensitization rate (and therefore possibly the prevalence of pollinosis) may be higher in urban rather than in rural areas in Japan (Kaneke et al., 2005), even though pollen dispersion might actually be lower in urban areas (Ishibashi et al., 2008), has led to the suggestion that the effects of air pollutants may be important when it comes to understanding the impact of pollen aeroallergens on the occurrence of allergic disease in this setting (Ishibashi et al., 2008; Nakae and Baba, 2010; Williams, 2005). Some support for this notion comes from earlier epidemiological studies which showed that long-term exposure to fine particulate matter (PM_{2.5}) was associated with an increased prevalence of hay fever among children in the US (Parker et al., 2009) and in Germany (Morgenstern et al., 2008). However, a follow-up study of these latter children did not support positive associations consistently at older ages (Fuertes et al., 2013), while a recent meta-analysis of several European birth cohorts also failed to find any link between air pollution and allergic sensitization (Gruzdeva et al., 2014). Similarly, an earlier study that targeted adults in Germany also found no significant association between the regional concentration of PM_{2.5} and allergic sensitization in urban areas (Bedada et al., 2007).

The idea that air pollutants may have the potential to affect the allergenicity of pollen has been raised by a number of authors previously (D'Amato, 2000, 2002; D'Amato et al., 2010). It has been suggested for example, that air pollution might be interacting with pollen grains to increase the bioavailability of pollen allergens of a different allergenicity (Ghani et al., 2012; Knox et al., 1997; Motta et al., 2006; Wang et al., 2012). It is also possible that air pollutants might facilitate pollen grains' penetration into the respiratory system (D'Amato et al., 2005). In particular, some evidence indicates that particulate matter has an

inflammatory effect on the airways and thus enhances the allergic response in individuals susceptible to pollen allergens (D'Amato et al., 2007).

Gaining a better understanding of the association between air pollution and pollen in terms of subsequent health outcomes may therefore be an important research task. Despite this, to the best of our knowledge, no previous study has examined whether there might be an interaction effect between airborne pollen and air pollution, e.g., if the effect of pollen on allergic disease is greater when there is a higher concentration of particulate matter. This is an important research gap, especially given the fact that Makra et al. (2013) found that in Hungary, the strongest correlations between patient numbers and pollutants were during the *Ambrosia* pollen season compared to the non-pollen season. This may be indicative of an interactive relation between pollen and air pollutants as reflected in poorer health outcomes.

Against this background and building on earlier research which has shown that both airborne pollen (Annesi-Maesano et al., 2012; Ross et al., 1996; Zhang et al., 2012) and air pollutants (Makra et al., 2013; Zhang et al., 2011) are independently associated with medical consultations for allergic respiratory disease, the aim of the current study was to examine both exposures simultaneously to see whether there is a significant interaction between airborne pollen and particulate matter concentration on daily doctor consultations for pollinosis in Japan.

2. Materials and methods

2.1. Clinic visit data

The current study was undertaken in Tokyo, Japan. Like other areas in Japan, the city has experienced a sharp growth in the number of cases of pollinosis in recent years, with its prevalence among the population rising from 18.2% to 28.2% in the period between 1996 and 2006 (Nishihata et al., 2010). We obtained the daily number of consultations for pollinosis (ICD-10, J30.1) from January to May, 2001–2011, from a general practice in the Chiyoda ward of Tokyo (Fig. 1). The medical data were compiled by the same physician using the same criteria throughout the study period for consistency. The study included only the initial consultations with clinical symptoms of pollinosis in a given year, to capture the onset of allergic symptoms during the pollen season. Revisits which were mainly for prescription refills were excluded. Based on interviews and intranasal observation, pollinosis was diagnosed if a patient met two conditions: (1) if they had a prior diagnosis of pollinosis or exhibited nasal symptoms every year during the Japanese cedar pollinosis season; and (2) during the clinic visit they were sneezing, had a running or blocked nose, without signs of other diseases such as the common cold, i.e. fever, sore throat, headache, being present (Nishihata and Saito, 2012). When required specific IgE tests were conducted, otherwise the specific variety of pollinosis (i.e. as being due to Japanese cedar or Japanese cypress pollen) was not differentiated, which was the case for most of the patients. Visits for prophylactic treatment without presentation of pollinosis-related symptoms and revisits for pollinosis treatment were excluded (Nishihata and Saito, 2012). Ethical approval for the study was obtained from the Ethics Committee of the Graduate School of Medicine, the University of Tokyo.

2.2. Pollen data

Daily measurements of the concentration of pollen were available from the Tokyo Metropolitan Institute of Public Health at 9 monitoring locations (Fig. 1) selected to represent the exposure level of patients living in, and commuting to Tokyo from the surrounding areas. The density of pollen from *Cryptomeria japonica* and *Chamaecyparis obtusa* (respectively known as the Japanese cedar and Japanese cypress, or *sugi* and *hinoki* in Japanese) was measured using the Durham method, which involves counting the number of pollen grains that become attached each day (24 h) to a vaseline coated glass slide, fixed inside a

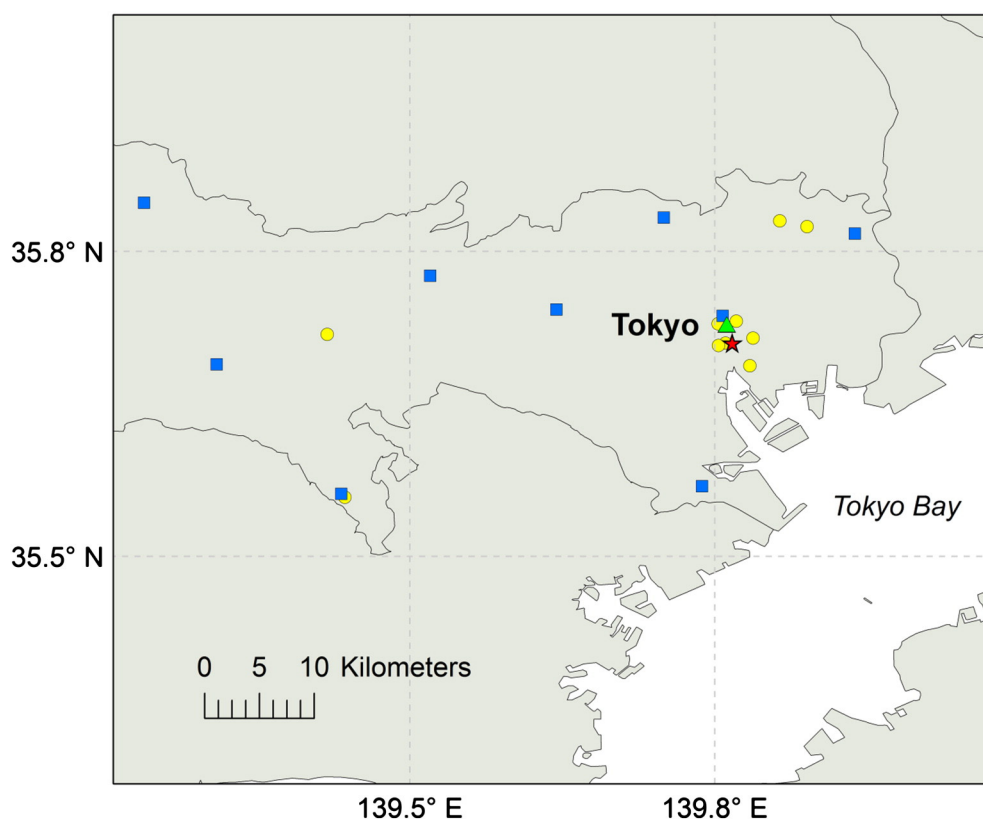


Fig. 1. Map of the study location and monitoring stations for pollen, air quality, and weather data. The location of the clinic is denoted by a star; pollen sampling stations are denoted by rectangles; air quality monitoring stations are denoted by circles; the meteorological station is denoted by a triangle.

Durham sampler (Kishikawa et al., 2009). The airborne pollen concentration is expressed as the number of pollen grains per cm^2 on the glass slide during each 24 hour period. Pollen counts measured with Durham samplers have been shown to correlate highly ($r > 0.92$; $P < 0.03$) with those collected using the Burkhard method of volumetric sampling which is the international standard (Kishikawa et al., 2009). Vaseline coated glass slides for collecting pollen grains were retrieved daily from the samplers for processing except on weekends. Readings for Friday, Saturday, and Sunday were computed as the averages of the 3-day accumulated pollen count. The proportion of days with missing values ranged from 0.18 to 0.24% of the total study period of 1663 days. Readings from the monitoring stations were highly correlated (Spearman's ρ s 0.90–0.95). Daily averages of the pollen count were computed using measurements from these stations.

2.3. Environmental data

Hourly data for fine particulate matter ($\text{PM}_{2.5}$) and suspended particulate matter (SPM) measured in $\mu\text{g}/\text{m}^3$ were acquired from the Environmental Database provided by the National Institute for Environmental Studies, Japan. Under the current Japanese Air Quality Standard, $\text{PM}_{2.5}$ is defined as particles collected with a 50% efficiency cut-off with an aerodynamic diameter of $2.5 \mu\text{m}$, while SPM refers to particles collected with an upper 100% cut-off at $10 \mu\text{m}$ aerodynamic diameter. For comparison, SPM has a diameter of approximately $7 \mu\text{m}$ when based on a 50% cut-off. To obtain the citywide average concentration, highly correlated daily 24-h mean values for $\text{PM}_{2.5}$ and SPM obtained from multiple national and local authority-managed monitoring facilities were averaged (Fig. 1). This calculation excluded days with more than 5 missing hourly values and stations with 30 or more missing daily values per year (i.e., 12.4 and 5.9 days were excluded per station every year for the computation of daily mean $\text{PM}_{2.5}$ and SPM, respectively). Measurements of gaseous pollutants such as ozone (O_3 ; ppbv),

sulfur dioxide (SO_2 ; ppbv), nitrogen dioxide (NO_2 ; ppbv), and carbon monoxide (CO ; ppmv) were also obtained to examine their potential confounding or intermediate effect when studying the modifying effect of airborne particles on the pollen-pollinosis relationship.

Meteorological data were obtained from the Japan Meteorological Agency. Hourly surface temperature and relative humidity monitored at the nearest weather station located approximately 2 km away from the medical facility were retrieved to compute the daily 24-h averages (Fig. 1).

2.4. Statistical analysis

We conducted a time-stratified case-crossover analysis to examine the potential effect modification of $\text{PM}_{2.5}$ and SPM on the association between airborne pollen counts and daily medical consultations for pollinosis (Levy et al., 2001). The case-crossover design was originally developed to circumvent the bias of control selection in a study that examined the onset of myocardial infarction (Maclure, 1991). It has since been widely adopted in studies related to the health effects of air pollution (Carracedo-Martinez et al., 2010). In a case-crossover design, only the cases are sampled and they serve as their own controls. For each case, the exposure periods before or after a disease (or both) are selected as the matched “control” periods and the distribution of these referent periods is compared with the exposure level at the time of the disease, that is, the diagnosis of pollinosis. To select time-stratified referents, we first divided the study period into monthly strata. For each case, the same days of the week within each stratum were chosen as controls. With this approach, the day-of-the-week, long-term, and seasonal effects are adjusted for by design.

To understand the modifying role of particulate matter in the association between pollen and pollinosis, we fitted a conditional logistic regression model to estimate the effect of pollen on different levels of particulate matter. Specifically, we divided $\text{PM}_{2.5}$ and SPM into 3 levels

using upper (95th) and lower (5th) percentile cut-off points to denote the high and low levels of concentration. The effect of pollen was then stratified using the method described in Roberts (2004), which has since been adopted in air pollution studies (Cheng and Kan, 2012; Ren et al., 2008). The heterogeneity of the pollen effects was assessed across different strata of particulate matter using different cut-off points to examine the sensitivity of our results. We tested the statistical significance of the difference between the stratified pollen effects (e.g., the pollen effect estimate when there was a high level of PM_{2.5} vs. the estimate when there was a moderate level) by calculating the 95% confidence interval (CI) using the method employed by Zeka et al. (2006). This method of examining the effect of an exposure across different levels of a covariate allows us to understand the interaction between the two.

The delayed effects of pollen were evaluated by examining a single-day lag and cumulative effects. Based on our initial exploratory analysis, the magnitude of the single-day lag effect for pollen, PM_{2.5}, and SPM remained positive up to the previous day 5 (not shown). Hence, we reported the estimates of the pollen effect from lag 0 to lag 5. To estimate the cumulative effect, daily concentrations from the current to the previous 5 days (i.e., lag 0 to lag 5) were included in the regression as a mean value. The non-stratified effects of pollen were also computed for comparison. We also fitted bi-pollutants models by inserting other gaseous pollutants one at a time to check the stability of the estimates. All models were adjusted for particulate matter (explicitly, lag 0 to 5 of either PM_{2.5} or SPM, constrained as a mean), daily mean temperature, relative humidity, and their 3-day delayed effects using a natural spline with 3 degrees of freedom.

To assess the pollen-adjusted association between particulate matter and the daily frequency of new pollinosis cases across different levels of pollen concentration, we estimated the effects of PM_{2.5} and SPM across a range of cut-off values from the 75th to 95th centiles of the observed daily concentration of pollen (which corresponded to a count of 21 to 227 per cm²). This analysis shows the risk characteristics of PM_{2.5} and SPM in relation to the daily new consultations under varying levels of pollen after removing the main effect of pollen, which can provide additional information on the current recommendations for prevention.

Results were expressed as the percentage change in daily new cases of pollinosis for an interquartile increase in the concentration of daily pollen. Statistical analyses were performed with the SAS statistical software package (version 9.3; SAS Institute Inc., Cary, NC, USA) and R (version 2.14.2; R Project for Statistical Computing, Vienna, Austria).

3. Results

There were 11,713 new consultations for pollinosis with an average of 10.6 daily new cases and a range of (0, 104) during the study period

Table 1
Summary of the daily concentration of airborne pollen counts, air pollutants and meteorological variables, 2001–2011.

	Min	P5	P25	Median	P75	P95	Max
Pollen counts (grain/cm ²) ^a	0	0	0	1.2	20.8	113.1	226.8
Air pollutant							
PM _{2.5} (μg/m ³)	2.0	7.3	11.9	17.8	25.1	38.0	79.4
SPM (μg/m ³)	5.6	12.9	20.1	28.1	39.0	60.0	124.8
SO ₂ (ppbv)	0.7	1.1	1.9	2.9	4.3	7.7	24.7
NO ₂ (ppbv)	10.4	20.5	30.9	37.8	44.4	55.2	83.8
CO (ppmv)	0.3	0.4	0.6	0.7	0.9	1.2	2.6
O ₃ (ppbv)	1.0	4.9	12.3	20.1	27.5	39.4	54.9
Weather							
Temperature (°C)	0.5	4.0	6.6	10.3	16.1	21.1	26.3
Relative Humidity (%)	22	29	40	52	64	80	88

P5: 5th percentile; P25: 25th percentile; P75: 75th percentile; P95: 95th percentile.
ppbv: parts per billion by volume; ppmv: parts per million by volume.

^a Includes both *Cryptomeria japonica* (sugi) and *Chamaecyparis obtusa* (hinoki).

after excluding public holidays, weekends and other non-consultation days. The distributions of air pollutants, temperature, and relative humidity from January to May, 2001–2011, are given in Table 1. Fig. 2 shows the average daily distribution of the pollen count, new cases of pollinosis, PM_{2.5}, and SPM for the study period. When PM_{2.5} was stratified by its 95th and 5th centiles, there were 9.0, 9.1, and 7.3 consultations for pollinosis per day on average during high, moderate, and low levels of PM_{2.5}, respectively. For SPM, the number of daily average consultations was 11.5, 9.3, and 6.7, respectively. PM_{2.5}, SPM, SO₂, NO₂, and CO were highly correlated with each other, but were negatively correlated with O₃ (Table 2). PM_{2.5} and SPM were positively correlated with temperature and humidity. Daily pollen concentrations generally showed a weak correlation with air pollutants and weather conditions (Table 2).

For an interquartile increase in daily pollen concentration (i.e., approximately 21 grains per cm²), the percentage increase in new daily cases of pollinosis was significantly positive for lag terms up to lag 4 or 5, depending on the level of PM_{2.5} and SPM (i.e., high, moderate, or low) (Table 3). The percentage increase was significantly higher at lag 0, 1, and 4 in the high PM_{2.5} stratum when compared to the estimates in the moderate stratum as indicated by the significant *P* values for the comparison between the two strata (i.e., high vs. moderate) (Table 3). When the level of PM_{2.5} was low, the percentage increase was significantly larger for lag 1 to 3 vis-à-vis the estimates during the period when the level of PM_{2.5} was moderate, denoted by the significant *P* values for the comparison of effect estimates between the moderate and low strata. When the pollen effect was stratified according to the SPM concentration, the percentage increase in the low stratum was significantly larger from the current day up to lag 3 versus the estimates in the moderate stratum.

The cumulative effect of pollen (the average of lag 0 to 5) was largest when the level of PM_{2.5} was high (Table 4). These results remained stable after adjustment for other air pollutants. These estimates were based on an interquartile increase of approximately 28 pollen grains per cm² on average on the current day and the preceding 5 days. When the cumulative effect of pollen was stratified according to SPM, the estimates in the different SPM strata were not significantly different from each other. When the level of PM_{2.5} or SPM was low, the magnitude for the cumulative effect of pollen tended to be higher when O₃ was included. When different centiles were used to demarcate the upper and lower level of PM_{2.5} and SPM (besides the 95th and 5th centiles), the estimates for the cumulative effect of pollen were always higher for the high level of PM_{2.5} (10.30 to 13.80%) in comparison to the estimates when the concentration was moderate (6.70 to 8.04% in Table 5). The same was observed in the cumulative effects stratified by levels of SPM with an upper cut-off value of the 90th centile or

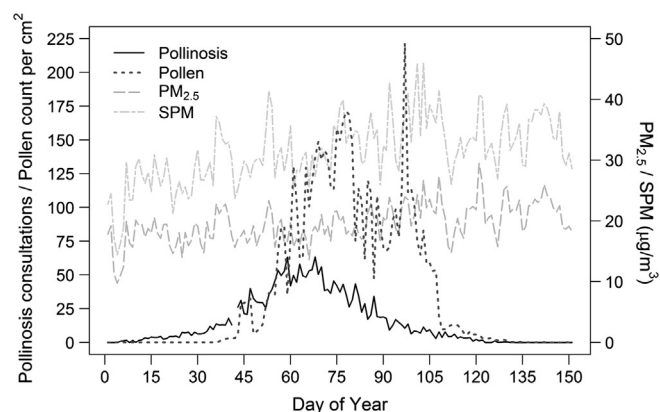


Fig. 2. Daily frequency of consultations for pollinosis, pollen count, concentration of fine particulate matter (PM_{2.5}) and suspended particulate matter (SPM) from January to May, 2001–2011. The mean values over the study period are shown. Weekends and public holidays are excluded from the mean calculation.

Table 2

Spearman correlation coefficients for the daily concentration of pollen, air pollutants, temperature, and humidity.

	PM _{2.5}	SPM	SO ₂	NO ₂	CO	O ₃	Temperature	Humidity
Pollen	0.09 [†]	0.14*	0.02	0.05	−0.07	0.21*	0.07	−0.07*
PM _{2.5}		0.92*	0.70*	0.64*	0.61*	−0.09*	0.39*	0.21*
SPM			0.62*	0.65*	0.57*	−0.12*	0.44*	0.38*
SO ₂				0.57*	0.58*	−0.19*	0.24*	−0.05
NO ₂					0.78*	−0.55*	0.05	0.09*
CO						−0.64*	−0.11*	0.06 [†]
O ₃							0.54*	−0.04 [†]
Temperature								0.38*

[†] $P < 0.05$.* $P < 0.01$.

lower. The estimated effects of pollen in the low PM_{2.5} stratum were also higher than the estimates in the moderate stratum, but they were not as evident in the estimates by SPM level.

4. Discussion

The present study showed that there was a significant interaction between the effects of airborne pollen and the air pollutants PM_{2.5} and SPM on daily medical consultations for pollinosis in Tokyo. The cumulative effects of pollen (average of lag 0 to 5) on consultations were significantly stronger at high levels of PM_{2.5} and SPM compared to the effects at moderate particulate matter levels. Moreover, this interaction was more robust for PM_{2.5} compared to SPM as witnessed by significant differences between high and moderate particulate matter levels across all cut-off points (Table 5). This difference in the cumulative effect of pollen between the two classifications of particulate matter remained even after adjusting for other air pollutants (Table 4).

Earlier research showed that increased respiratory allergy/hay fever symptoms were associated with long-term exposure to increased levels of PM_{2.5} and PM_{2.5–10} among US children aged between 3- and 7-years old (adjusted odds ratio per 10 $\mu\text{g}/\text{m}^3 = 1.23$; 95%CI, 1.04–1.46 for PM_{2.5} and 1.13; 95%CI, 1.05–1.22 for PM_{2.5–10}) (Parker et al., 2009), while the median (interquartile range) of PM_{2.5} concentration was 13.1 (10.9–15.2) $\mu\text{g}/\text{m}^3$, which was slightly lower than the concentration in the current study. Long-term exposure to higher PM_{2.5} was also significantly associated with hay fever and pollen allergy sensitization among children aged 4 to 6 living in Germany (Morgenstern et al., 2008), where the median (interquartile range) of annual average PM_{2.5} concentration was 11.0 (10.5–11.5) $\mu\text{g}/\text{m}^3$, which was again lower than the level observed in the present study. Additionally, a London-based

study found a positive association between high PM₁₀ levels and daily medical consultations for allergic rhinitis (Hajat et al., 2001). The findings from these earlier studies together with those from the current study suggest that the stronger effect of the cumulative airborne pollen count on consultations we observed on high-PM_{2.5}/SPM days might be indicative of the synergetic effect of both types of particulate matter and pollen allergens resulting in worsened pollinosis symptoms (D'Amato et al., 2014; Ghiani et al., 2012; Wang et al., 2014). If this supposition is correct, it is an important finding as despite the numerous previous studies on the effects of air pollution on allergic disorders, to the best of our knowledge, the current study is the first to show an interactive relation between particulate matter and airborne pollen concentrations in terms of daily medical consultations for an allergic disorder. Some support for our finding that high levels of PM_{2.5} might be especially detrimental for allergic disorders comes from a previous study which showed that even a short-term (48 h) exposure to a higher concentration of PM_{2.5} was associated with more severe inflammation of the nasal passage among urban asthmatic children (Nikasinovic et al., 2006).

While a significant interaction was observed between pollen and both PM_{2.5} and SPM, this interaction was stronger and more robust for PM_{2.5} compared to SPM (Table 5). One study targeting US children similarly reported that the association between long-term exposure to PM_{2.5} and the prevalence of hay fever was stronger than that between long-term exposure to PM_{2.5–10} and hay fever (Parker et al., 2009). Although determining which factors underlie the variation observed in these relations is a matter for future research, it can be speculated that they may be associated with differences in the composition of these particulate matter types. Specifically, the idea has been advanced that airborne pollen grains might be able to bind to smaller particulate

Table 3

Estimates for the single-day effect of pollen as percentage changes in daily new pollinosis cases for an interquartile increase of daily pollen concentration at high, moderate and low levels of particulate matter defined using the 95th and 5th centiles as cut-points.

Lag term for the pollen variable ^a	(A) High		(B) Moderate		(C) Low		(A–B) P value	(B–C) P value	Unstratified Pollen model	
	Change (%)	95%CI	Change (%)	95%CI	Change (%)	95%CI			Change (%)	95%CI
By PM _{2.5} level										
0	4.21	(3.25, 5.18)	2.30	(1.92, 2.69)	3.51	(0.82, 6.27)	<0.01	0.39	2.43	(2.05, 2.80)
1	5.67	(4.46, 6.89)	3.58	(3.23, 3.94)	5.01	(3.89, 6.14)	<0.01	0.02	3.71	(3.36, 4.06)
2	4.10	(3.12, 5.10)	3.66	(3.30, 4.03)	8.85	(6.37, 11.40)	0.42	<0.01	3.74	(3.39, 4.09)
3	3.90	(2.92, 4.88)	3.08	(2.72, 3.45)	5.70	(3.74, 7.70)	0.13	0.01	3.19	(2.83, 3.54)
4	3.31	(2.35, 4.29)	2.01	(1.64, 2.37)	1.20	(0.40, 2.00)	0.01	0.07	2.00	(1.67, 2.33)
5	1.62	(0.36, 2.89)	1.41	(1.03, 1.79)	0.44	(−0.43, 1.31)	0.77	0.04	1.29	(0.93, 1.65)
By SPM level										
0	3.27	(2.31, 4.25)	2.34	(1.97, 2.72)	9.63	(6.14, 13.25)	0.08	<0.01	2.25	(1.89, 2.62)
1	3.97	(2.69, 5.26)	3.48	(3.14, 3.82)	5.47	(4.21, 6.75)	0.48	<0.01	3.52	(3.18, 3.86)
2	2.65	(1.69, 3.61)	3.43	(3.08, 3.78)	12.43	(9.68, 15.25)	0.13	<0.01	3.44	(3.10, 3.78)
3	2.84	(1.85, 3.84)	2.85	(2.49, 3.21)	10.97	(8.47, 13.52)	0.98	<0.01	3.93	(2.58, 3.27)
4	2.21	(1.22, 3.20)	1.69	(1.34, 2.05)	1.30	(0.51, 2.10)	0.34	0.39	1.68	(1.36, 2.00)
5	−1.25	(−2.57, 0.09)	1.26	(0.88, 1.64)	0.61	(−0.25, 1.48)	<0.01	0.18	1.05	(0.70, 1.40)

^a All models were adjusted for particulate matter (lags 0–5 constrained as an average), temperature, humidity, and the delayed effects of temperature and humidity (lags 0–3 constrained as an average).

Table 4
Estimates for the 5-day cumulative effect of pollen as percentage changes in daily new pollinosis cases for an interquartile increase of daily pollen concentration at high, moderate and low levels of particulate matter defined using the 95th and 5th centiles as cut-points.

Model ^a	(A) High		(B) Moderate		(C) Low		(A–B) P value	(B–C) P value	Unstratified Pollen model	
	Change (%)	95%CI	Change (%)	95%CI	Change (%)	95%CI			Change (%)	95%CI
By PM _{2.5} level										
PM _{2.5} only	10.30	(8.48, 12.16)	8.04	(7.28, 8.81)	7.97	(5.87, 10.11)	0.02	0.96	8.20	(7.46, 8.95)
PM _{2.5} + SO ₂	10.22	(8.39, 12.08)	8.12	(7.36, 8.88)	7.57	(5.47, 9.67)	0.04	0.65	8.25	(7.51, 9.00)
PM _{2.5} + NO ₂	11.69	(9.82, 13.58)	8.79	(8.01, 9.58)	8.54	(6.37, 10.71)	<0.01	0.85	8.98	(8.22, 9.76)
PM _{2.5} + CO	11.48	(9.61, 13.39)	8.61	(7.83, 9.40)	8.66	(6.51, 10.81)	<0.01	0.97	8.81	(8.05, 9.58)
PM _{2.5} + O ₃	10.49	(8.65, 12.36)	8.02	(7.25, 8.79)	10.06	(7.85, 12.27)	0.02	0.09	8.28	(7.53, 9.04)
By SPM level										
SPM only	7.40	(5.59, 9.24)	7.64	(6.89, 8.40)	8.60	(6.44, 10.80)	0.82	0.42	7.67	(6.94, 8.41)
SPM + SO ₂	7.27	(5.47, 9.11)	7.67	(6.92, 8.42)	8.40	(6.25, 10.59)	0.71	0.54	7.68	(6.94, 8.41)
SPM + NO ₂	8.54	(6.70, 10.41)	8.04	(7.27, 8.81)	9.38	(7.19, 11.62)	0.64	0.26	8.13	(7.38, 8.88)
SPM + CO	8.01	(6.18, 9.87)	7.88	(7.12, 8.65)	8.85	(6.68, 11.06)	0.91	0.42	7.93	(7.18, 8.68)
SPM + O ₃	7.80	(5.98, 9.65)	7.51	(6.75, 8.27)	10.38	(8.14, 12.66)	0.78	0.02	7.64	(6.90, 8.39)

^a All models included the main effect of pollen (lags 0–5 constrained as a mean) and are adjusted for particulate matter (lags 0–5 constrained as an average), temperature, humidity, and the delayed effects of temperature and humidity (lags 0–3 constrained as an average). Bi-pollutant models contained an additional variable for air pollutant with the same mean-constrained lag term up to lag 5.

matter (D'Amato et al., 2007), with previous research from Japan indicating that there are airborne particles smaller than 0.3 μm that may contain Japanese cedar pollinosis allergens, i.e. Cry j 1 and Cry j 2 (Takahashi et al., 1991). If this is correct, it is possible that in terms of the present study these allergens might have been bound to PM_{2.5} to create a highly allergenic source which had a stronger effect at higher concentration levels as reflected in a greater number of allergic health outcomes.

The potential effects of diesel exhaust particles (DEP) should also be taken into account in this respect when considering the findings from the current study. More than 90% of DEP have a diameter smaller than 1 μm and they are the major contributor to PM_{2.5} (Salvi and Holgate, 1999). In addition, there is some evidence that they may also exacerbate the effects of allergens by enhancing airway inflammation and IgE-mediated responses (Chehregani and Kouhkan, 2008; D'Amato et al., 2005; Wang et al., 2012). Individuals coming into contact with DEP combined with ragweed allergen have been found for example, to have markedly higher ragweed-specific IgE compared to those individuals solely exposed to ragweed allergen (Diaz-Sanchez et al., 1997), while ragweed pollen collected along roads with a heavy volume of traffic has been reported as having a higher whole allergenicity than pollen from roads with less traffic or in greener areas (Ghani et al., 2012).

It was also noteworthy that we observed a significant synergetic effect between airborne pollen and concentrations of both PM_{2.5} and SPM, although the median values for the concentrations of both

stratifications of particles were well below the legally permitted limits as determined by the (24-hour mean) air quality standard in Japan i.e. 17.8 vs. 35 $\mu\text{g}/\text{m}^3$ for PM_{2.5} and 28.1 vs. 100 $\mu\text{g}/\text{m}^3$ for SPM (Ministry of the Environment, 2014) (Table 1 and Fig. 2). Our results thus indicate that these particles can interact with pollen antigens to worsen pollinosis symptoms even at levels that are deemed safe in terms of air quality standards.

The observed significantly positive lag effect of airborne pollen (Table 3) might be explained by the findings from several earlier studies, which offer a clue as to what may be happening and point to the potentially important airborne role of Cry j 1, the major allergen for pollinosis. The presence of Cry j 1, even at a very low concentration (1 to 3 pg/m^3), is believed to trigger Japanese cedar pollinosis symptoms, which might explain why there is evidence that in Japan the majority of pollinosis patients start experiencing symptoms a few weeks before a noticeable amount of airborne pollen is observed each season (Takahashi et al., 2007). The peak micron-size Cry j 1 concentration is observed a few days after the peak concentration of intact pollen in the air, because micron-size particles continue to remain airborne for some time after intact pollen grains have descended to the ground (Takahashi et al., 1991). In addition, although intact Japanese cedar pollens, which are the major carriers of allergens, are about 29 μm to 40 μm in diameter (Takahashi et al., 1995), pollen-free Cry j 1 can attach to particles with a diameter of less than 0.3 μm (Takahashi et al., 1991) which accords with the notion that has been previously advanced that DEP can

Table 5
Estimates for the cumulative effect of pollen as percentage changes in daily new pollinosis cases per interquartile increase of daily pollen concentration on the current and 5 previous days at high, moderate and low levels of particulate matter with varying centile cut-offs.

Percentile cut-offs for air pollutant ^a	(A) High		(B) Moderate		(C) Low		(A–B) P value	(B–C) P value
	Change (%)	95%CI	Change (%)	95%CI	Change (%)	95%CI		
By PM _{2.5} level								
95–5	10.30	(8.48, 12.16)	8.04	(7.28, 8.81)	7.97	(5.87, 10.11)	0.02	0.96
90–10	12.07	(10.38, 13.79)	7.95	(7.20, 8.71)	9.52	(7.67, 11.39)	<0.01	0.12
85–15	11.48	(9.89, 13.09)	7.84	(7.09, 8.60)	11.84	(10.22, 13.49)	<0.01	<0.01
80–20	11.90	(10.28, 13.53)	7.50	(6.73, 8.27)	12.23	(10.86, 13.61)	<0.01	<0.01
75–25	13.80	(12.35, 15.27)	6.70	(5.89, 7.53)	10.64	(9.57, 11.71)	<0.01	<0.01
By SPM level								
95–5	7.40	(5.59, 9.24)	7.64	(6.89, 8.40)	8.60	(6.44, 10.80)	0.82	0.42
90–10	9.60	(8.09, 11.14)	7.55	(6.81, 8.30)	7.90	(6.15, 9.67)	0.02	0.74
85–15	9.81	(8.37, 11.26)	7.35	(6.60, 8.12)	9.02	(7.52, 10.54)	<0.01	0.05
80–20	10.28	(8.87, 11.71)	7.37	(6.61, 8.13)	8.67	(7.34, 10.01)	<0.01	0.10
75–25	10.91	(9.59, 12.25)	6.67	(5.90, 7.46)	9.93	(8.75, 11.13)	<0.01	<0.01

^a All models are adjusted for particulate matter (lags 0–5 constrained as an average), temperature, humidity, and the delayed effects of temperature and humidity (lags 0–3 constrained as an average).

absorb aeroallergens from pollen grains and facilitate the continued airborne presence of the allergen (D'Amato et al., 2005). Taking these factors together, it can be hypothesized that the airborne pollen concentration on previous days might be associated with the current day's level of pollinosis antigens in the air which thus results in the observed lagged effect of pollen counts, even after adjustments are made for the current day's level of airborne pollen. The observed significant single-day lag effects of airborne pollen on days with a low PM_{2.5} or SPM concentration, compared to days with moderate particulate matter concentrations (Table 3), suggests further studies are needed to determine if this result reflects a true biological phenomenon caused by factors not accounted for in the present study.

There are some limitations that should be borne in mind when considering the findings from this study. We included only one clinic in Tokyo which limits the generalizability of the results. Further studies that target children and adults residing in other regions in Japan will be required to see if these findings are replicated elsewhere. Moreover, the patients of this clinic also included adults who commuted to Tokyo from surrounding areas for their work (according to data from 2011 the proportion of such patients accounted for 34% of the total number of first-time visits in that year). Given this, it is possible that the pollen and air pollution readings used in the current study might not fully reflect exposure levels, although potential variation in individual exposure to airborne matter is a problem that is common to this type of research more generally. Despite these potential limitations we nevertheless found a significant interactive effect between airborne pollen and particulate matter on the daily number of pollinosis consultations, which can be explained by biologically plausible mechanisms.

5. Conclusion

Using data for the period from 2001 to 2011, this study found that there was an interactive effect between particulate matter and airborne pollen as reflected in an increased number of daily medical consultations for pollinosis in Tokyo. The lagged effect of airborne pollen points to the potentially important role of pollen allergens which might remain in the air for a longer period than pollen grains, possibly due to their interaction with air pollutants such as PM_{2.5}. Studies which focus on the measurement of pollen allergens that encompass wider regions in Japan are needed to further elucidate the interactive effects of particulate matter and pollen on cases of pollinosis at the national level.

Acknowledgments

This study was conducted as a part of the project entitled Development of a Seamless Chemical Assimilation System and its Application for Atmospheric Environmental Materials (SALSA), which is supported by a grant-in-aid from the Research Program on Climate Change Adaptation (RECCA) by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Ministry of the Environment (MOE) in Japan. The views expressed in the article are those of the authors and do not necessarily represent the view or policies of the aforementioned organizations.

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