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Effect of desert dust exposure on allergic symptoms A natural experiment in Japan

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ABSTRACT

Background: Desert dust originating from arid and semiarid areas is transported to widespread regions, including Japan. Desert dust particles exert adjuvant effects in animals.

Objectives: To examine whether desert dust enhances allergic symptoms in real-life settings and to explore its effect modifiers.

Methods: We conducted an observational study of 3,327 pregnant women during spring and fall in October 2011 to May 2013 in 3 regions in Japan as an adjunct study of the Japan Environment & Children's Study. We acquired participants' daily symptom scores by sending a questionnaire to their mobile phones on high desert-dust days ($>0.07/\text{km}$) and on some randomly selected other days (control days) for each participant.

Results: Pregnant women had an increased risk of allergic symptoms on high desert-dust days (adjusted odds ratio [OR], 1.10; 95% CI, 1.04–1.18). The increased OR was mostly driven by those who showed positive IgE to Japanese cedar pollen when pollen simultaneously dispersed (adjusted OR, 1.25; 95% CI, 1.13–1.38), whereas no clear risk increase was observed in the absence of pollen or for participants with negative IgE to Japanese cedar pollen. The risk elevation was observed from low levels of desert dust in a dose-dependent manner even on control days.

Conclusions: Ambient desert dust level was associated with an increased risk of allergic symptoms in pollen-sensitized pregnant women when pollen was present in the air. The risk increase was dose

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dependent and was observed from low levels of desert dust. These results support a hypothesis that ambient desert dust particles exert adjuvant effects in human in real-life settings.

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Introduction

Aerosol particles are produced by a variety of natural and anthropogenic processes. Desert dust constitutes approximately 35% of the aerosol mass injected into the troposphere.¹ Large quantities of desert dust are transported over the oceans from arid continental regions and are deposited globally.^{2–4} In addition to rock-forming and clay minerals, desert dust particles contain microbial agents, such as bacteria, fungi, and viruses,^{2,4–6} and anthropogenic atmospheric pollutants are likely absorbed during transport.⁷ Many toxicologic and controlled human exposure studies have found that particulate matter (PM) exposure alters the immune response to antigens, suggesting that PM may act as an adjuvant,⁸ which can modify (boost) the effects of allergens. Experiments in animal models have also found that desert dust particles aggravate antigen-induced allergic inflammation.^{9,10} However, few studies have assessed the relevance of these adjuvant effects in real-life settings.

In epidemiologic studies, desert dust events have been linked to health outcomes, such as the exacerbation of asthma or allergic rhinitis, with a subtle to clear risk elevation.^{11–13} It remains unknown why the estimated risk for outcomes, such as the worsening of asthma, varies across studies, with some studies suggesting associations between desert dust and respiratory and allergic outcomes and others not,^{14,15} but a number of effect modifiers might be involved, including differences in the size and composition of particles and the copresence of antigens or other air pollutants.

Asian dust originates from deserts in arid and semiarid areas of the Asian continent, such as the Gobi Desert and Loess Plateau, and is widely dispersed. In the spring and fall, heavy Asian dust blows eastward, sometimes reaching Japan, which is thousands of kilometers away from these arid regions, and gives the air a yellow hue for several days. During the spring, Japanese cedar pollen (JCP), the most common antigen for pollinosis in Japan, is also dispersed, affecting nearly half the population.¹⁶

In the present study, we focused on the partial overlap of pollen dispersal and Asian dust seasons to determine whether ambient desert dust exerts adjuvant effects, thereby enhancing the secondary immune response in real-life settings. To this end, we conducted an observational study spanning 4 Asian dust seasons during 2 years as the first part of an adjunct study of a national birth cohort in Japan (Japan Environment & Children's Study [JECS]).^{17,18} The study protocol is registered (UMIN000010826) and has been previously published.¹⁷

Methods

Design

This study was initiated in 2011 as the first part of an adjunct study of the JECS to examine the effects of desert dust exposure on allergic symptoms in pregnant women and on the development of asthma and other allergic diseases in their children in Kyoto, Toyama, and Tottori.^{17,18} The study protocol was approved by the ethics committees of Kyoto University, University of Toyama, and Tottori University.

On enrollment, baseline information, such as history of asthma and other allergic diseases, was collected via a web-based questionnaire sent to mobile phones. Various lifestyle parameters, including diet and housing environment, were obtained during the JECS, and serum IgE to common allergens was measured during the

first trimester of pregnancy. Details of these parameters are described elsewhere.^{17,18}

In the evening, when high desert dust was observed (Asian dust days), all participants in the observed area received a self-administered questionnaire regarding allergic symptoms (Allergy-Control-Score) and behavior during the day via their mobile phones.^{17,23,24} For comparison, an identical questionnaire was sent on non-high desert dust days during Asian dust seasons (February to May and October to November) to selected participants, with each participant having an approximately 10% probability on each non-high desert dust day to receive the questionnaire. That is, each participant received an identical questionnaire randomly on 1 control day for every 10 days during the Asian dust seasons. Participants were not informed if the day was an Asian dust day or control day.

Participants and Setting

Participants were pregnant women in the general community. The JECS participants from Kyoto, Toyama, and Tottori who provided written informed consent to participate in the adjunct study were enrolled. These areas are located in Western Japan, with Kyoto being in a basin and Toyama and Tottori facing the Sea of Japan. Each has urban, suburban, and rural areas. We focused only on pregnant women for 2 reasons. First, pregnant women are less likely to take medication, and therefore their allergic symptoms are less likely to be affected by medication. Second, we plan to investigate the effects of desert dust on their children in the future.

Exposure Measures

Asian dust days (high desert dust days) were a priori defined as days during which the light detection and ranging system (LIDAR) detected more than 0.07/km (ie, approximately 70 $\mu\text{g}/\text{cm}^3$ of total suspended matter of desert dust [12-hour median from 6:00 to 18:00] at a 135-m altitude based on previous reports).^{12,17,19} LIDAR is an optical remote sensing technology that measures scattered light properties to obtain information on a distant target. When used in combination with a polarization analyzer, it can distinguish nonspherical mineral dust particles (eg, desert dust) from spherical, nonmineral particulates emitted from human activities (eg, traffic-related pollutants).^{12,20–22}

Main Outcome Measures

The main outcome was the proportion of participants with any symptom (symptom score >0) as assessed by a self-administered questionnaire regarding allergic symptoms (Allergy-Control-Score).^{17,23,24} The questionnaire was sent to participants' mobile phones on the evenings of Asian dust days and control days during the study period, and participants answered the questionnaire using their mobile phones or personal computers within the set time limit (within 28 hours).

Statistical Analysis

The generalized estimating equations logistic regression analysis was used to evaluate the influence of Asian dust exposure.¹⁷ For the occurrence of any symptom (symptom score >0), we evaluated odds ratios (ORs) for effect measures that compare event occurrence risks between Asian dust days (dust level $\geq 0.07/\text{km}$) and control days (dust level <0.07/km) as the main analysis per

protocol.¹⁷ We also conducted the same analysis by dividing the control days into 3 dust-level categories based on the study period median of 0.01/km (<0.01/km, 0.01–0.04/km, and 0.04–0.07/km) to observe the effects of low dust levels. To account for correlations arising from repeated measurements of the same participant, we used robust SE estimates based on an exchangeable correlation matrix.

The following factors were examined as potential confounders¹⁷: local pollen levels; local sulfur dioxide, nitrogen dioxide, and ozone levels; levels of local spherical particulates (ie, particulates other than desert dust measured by LIDAR); and local climatic variables (air pressure and pressure change from the previous day, mean temperature and temperature change from the previous day, temperature change within the day, lowest temperature, and humidity) per protocol. Each pollutant was examined for its association with outcomes using threshold models with various cutoff values (the standard threshold for air pollution in Japan and the 95th, 90th, 75th, and 50th percentiles of the observed distributions), and the best model was determined based on quasi-likelihood under the independence model criterion values. Factors associated with outcomes ($P < .10$) were adopted as possible confounders.¹⁷ Pollen, other pollutants, and participant characteristics were evaluated by 2-factor model analysis with respective interaction terms¹⁵ to examine potential effect modifiers.

All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina). Additional details are provided in the [eMethods](#) and [eResults](#).

Results

Participant Characteristics

A total of 7,829 pregnant women had enrolled at JECS regional centers in Kyoto, Toyama, and Tottori by the end of May 2013. Of these, 4,691 (59.9%) provided consent to participate in the adjunct study, and 4,178 took part in the first part of the study (ie, investigation of the short-term effects of desert dust on pregnant mothers). Among these, 3,327 (79.6%) actually experienced Asian dust seasons (October to November 2011, February to May and October to November in 2012, and February to May in 2013) during their pregnancies and responded to the questionnaires ([Fig 1](#)). A total of 41,020 questionnaires were sent on the evenings of Asian dust days and control days, of which 29,434 (71.8%) were completed within the set time limit of 28 hours from receipt. Sixteen participants (0.5%) dropped out due to moving outside the study area, withdrawal of consent, or miscarriage by the end of May 2013 ([Fig 1](#)).

Participant characteristics are summarized in [eTables 1 and 2](#). All participants were pregnant and represented a wide age range, from teens to those older than 45 years, with various socioeconomic backgrounds. Participant characteristics were similar to those reported by the Japanese government in 2012, except that the proportions of current smokers and those with an educational level up to junior high school completion were lower than that in the government report.^{25–28} Levels of serum IgE to JCP were obtained for 92.7% of participants, of whom 57.2% tested positive (>0.35 IU/mL). Overall, the study cohort was considered a good representation of pregnant women in Japan.

Characterization of Exposure

Of the 363 days during the study period, there were 18, 4, and 5 Asian dust days, as defined in our study, in Kyoto, Toyama, and Tottori, respectively ([eFig 1](#)). Suspended particulate matter (SPM) and PM 2.5 μm or less in diameter (PM_{2.5}) concentrations on Asian dust days were more than 2-fold higher compared with those measured on control days ([eTable 3](#)). Correlation coefficients between desert dust and other air pollutants or climatic variables are

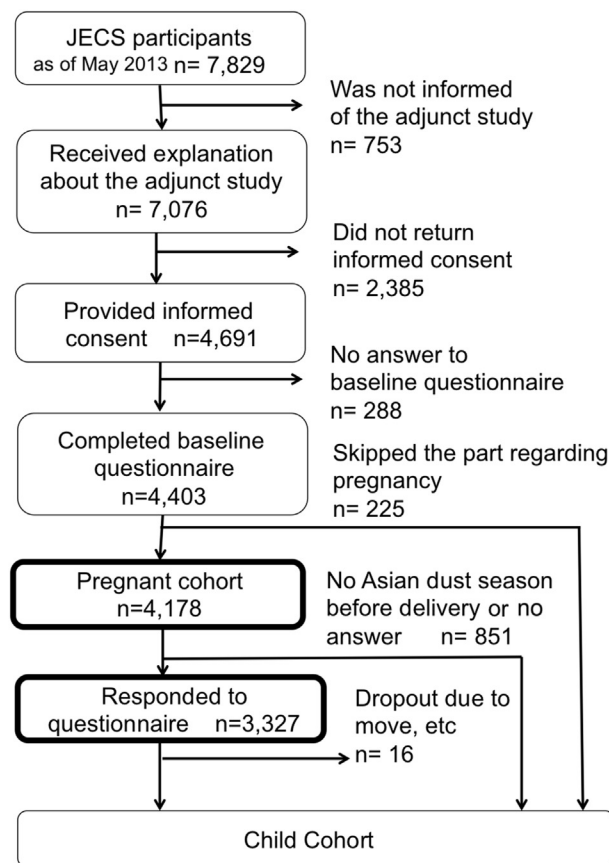


Figure 1. Participants in the Japan Environment & Children's Study (JECS) and the adjunct study as of May 2013.

given in [eTable 4](#). None of the variables revealed a particularly high correlation with desert dust.

Characterization of Symptoms

The occurrence of any symptom (symptom score >0) was reported in 2,543 (56.1%) of 4,374 responses on Asian dust days, 11,744 (46.9%) of 25,060 on control days, and 14,197 (48.2%) of 29,434 in total. The distribution of symptom scores is given in [eTable 5](#).

Association Between Desert Dust and Symptom Exacerbation

Generalized estimating equations logistic regression analysis with an exchangeable correlation matrix revealed that pregnant women developed symptoms more often on Asian dust days ($\geq 0.07/\text{km}$) than on control days (OR, 1.24, 95% confidence interval [CI], 1.16–1.32). After adjusting for other air pollutants, climatic variables, and various individual characteristics, the OR decreased relative to the crude model but remained significant (OR, 1.10; 95% CI, 1.04–1.18) ([Table 1](#)). An increased risk was observed even at low levels of desert dust (0.01–0.04/km; 0.01/km is the 50th percentile during the study period in the 3 regions) in a dose-dependent manner ([Fig 2](#)).

Effect Modifiers

We explored potential effect modifications of desert dust by duration spent outside on dust days, coexistence of pollen in the air on dust days, and participants' history of allergic and otolaryngologic diseases (allergic rhinitis, asthma, atopic dermatitis, chronic otitis media, chronic sinusitis), as well as IgE response to JCP or house dust mites. An increase in risk was evident for those who

Table 1ORs (95% CIs) for Any Allergic Symptom Development the in Adjusted Model^a

Symptom	OR (95% CI)	P Value
Desert dust (>0.07/km) ^a	1.10 (1.04–1.18)	.002
Sulfur dioxide (>3 ppb) ^a	1.17 (1.08–1.27)	<.001
Cedar or cypress pollen (>40/m ³) ^a	1.37 (1.28–1.47)	<.001
Lowest temperature of the day ^b	0.99 (0.98–0.99)	<.001
Temperature difference during the day ^b	1.01 (1.00–1.01)	.008
Humidity on the previous day ^b	1.00 (0.99–1.00)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Model was adjusted for smoking status of participants, smoking status of participants' partners, house incomes, age, and body mass index.

^aDesert dust, sulfur dioxide, and cedar or cypress pollen were treated as dichotomous (with a cutoff value of 0.07/km, 3 ppb, and 40/m³, respectively).^bClimatic variables were treated as numerical.

spent time outside on dust days (Fig 3). The OR for any symptom on Asian dust days for those who spent more than 10 minutes outside was 1.30 (95% CI, 1.20–1.40), whereas the same OR for those who spent less than 10 minutes outside was 1.15 (95% CI, 1.03–1.28). A dose-dependent increase in risk of any symptom was observed for positive serum IgE result to JCP when pollen was present in the air, whereas no clear increase in risk was observed in the absence of pollen or for participants with negative IgE results to JCP (Fig 4). The OR for any symptom on Asian dust days compared with control days was 1.48 (95% CI, 1.34–1.64), the adjusted OR was 1.25 (1.13–1.38) for those with positive IgE to JCP when pollen was present in the air, the OR was 0.95 (95% CI, 0.71–1.28) for those with IgE responses to JCP when pollen was not present, and the OR was 1.02 (95% CI, 0.92–1.14) for those with negative IgE results to JCP when pollen was present. Two-pollutant analysis with interaction terms of desert dust and pollen revealed a significant interaction (Table 2). Among potential effect modifiers examined, significant interaction effects were found for IgE to JCP, history of allergic rhinitis, and time spent outside (eTable 6 and eFig 2). See the eAppendix for lag effects (eFig 3) and comparisons with the effects of PM_{2.5} (eFig 4, eFig 6, and eFig 8) or SPM (eFig 5, eFig 7, and eFig 9), and the results of sensitivity analysis (eTable 7, eTable 8 and eTable 9).

Discussion

In this study, we found that pregnant women are more likely to develop allergic symptoms on Asian dust days compared with non-Asian dust days (adjusted OR, 1.10; 95% CI, 1.04–1.18). The

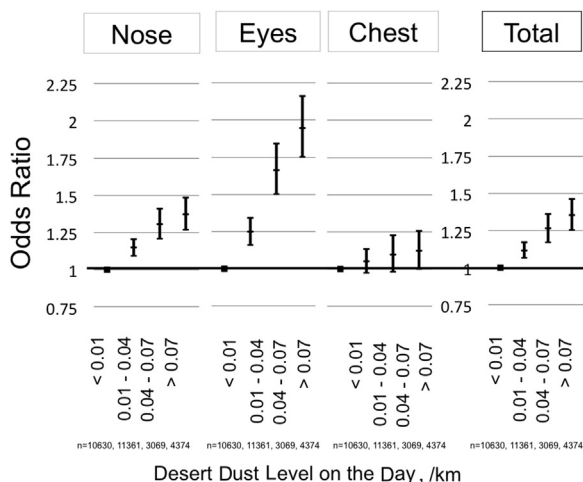


Figure 2. Crude odds ratios and 95% confidence intervals (error bars) for symptom development (symptom score >0) relative to days with less than 0.01/km desert dust (<50th percentile during the study period).

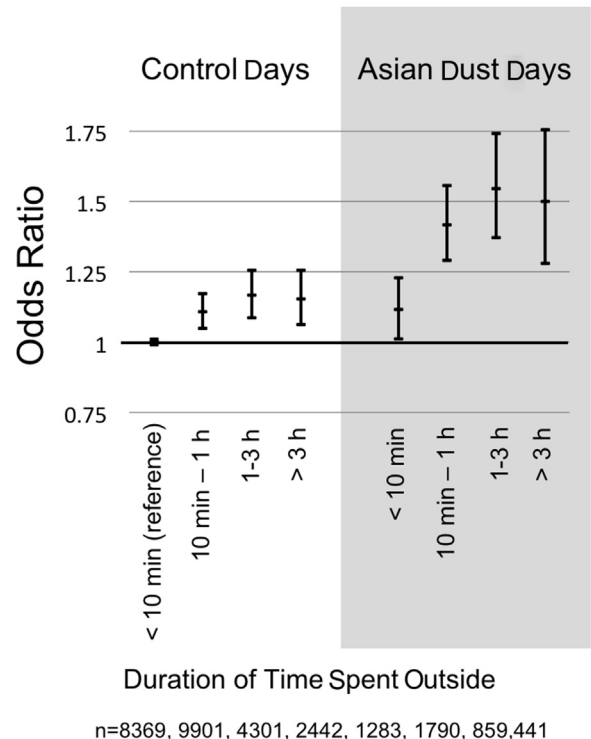


Figure 3. Crude odds ratios and 95% confidence intervals (error bars) for symptom development (symptom score >0) by duration of time spent outside on Asian dust days (>0.07/km) and control days.

increase in OR was mostly driven by participants with IgE responses to JCP when pollen was present in the air (adjusted OR, 1.25; 95% CI, 1.13–1.38), and no clear increase in risk was observed in the absence of pollen or for those with negative IgE results to JCP. A dose-dependent increase in risk was observed from low levels of desert dust even on nondust days.

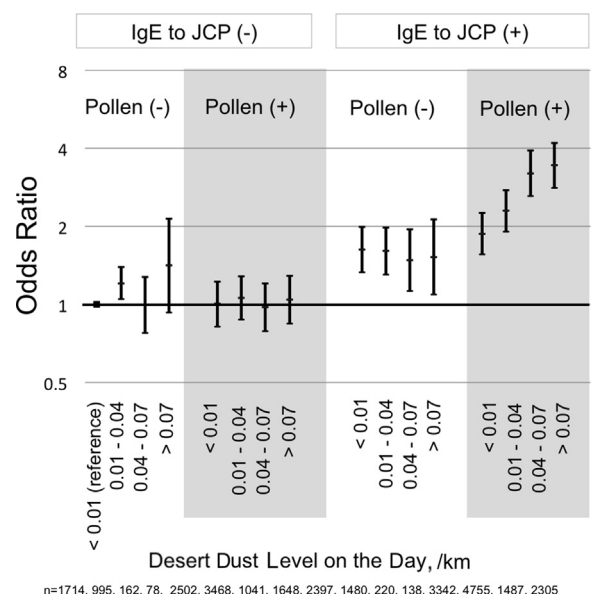


Figure 4. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by desert dust level, presence of ambient pollen, and serum IgE response to Japanese cedar pollen (JCP) (negative [-] or positive [+]), relative to days with less than 0.01/km desert dust (<50th percentile during the study period) without ambient pollen in participants with negative IgE results to JCP.

Table 2

β Estimation (95% CIs) With (Under) or Without (Upper) the Consideration of Interaction With Ambient Pollen Counts in 2 Pollutant Models^a

Model	β Estimate (95% CI)	P Value
Model 1		
Desert dust ^a	0.038 (0.000 to 0.075)	.049
Cedar or cypress pollen ^a	0.208 (0.161 to 0.255)	<.001
Model 2		
Desert dust ^a	−0.001 (−0.045 to 0.042)	.96
Cedar or cypress pollen ^a	0.331 (0.240 to 0.421)	<.001
Interaction term	0.085 (0.035 to 0.134)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

^aDesert dust and cedar or cypress pollen were log transformed with the addition of 0.0001 and 0.5 to the 0 value, respectively. Models were adjusted for smoking status of participants, smoking status of participants' partners, house incomes, age, and body mass index.

These results support a previous hypothesis derived from animal studies,⁹ that is, that desert dust exposure exacerbates allergic symptoms when antigens are simultaneously present, enhancing immune responses among those who are sensitized to these antigens. Allergic rhinitis is a major public health concern worldwide and currently affects approximately 20% to 30% of the global population.²⁹ The association with air pollution has attracted much attention, particularly in relation to fossil fuels and traffic-related pollutants. The present study found that desert dust–related particulates are also an important factor, especially in terms of future public health, given increasing evidence of increased dust formation due to desertification, climatic variability, and global warming.^{30–32} The mechanism underlying the adjuvant effects of desert dust may involve (1) a depot effect (antigen persistence and prolonged release)³³; (2) activation of innate immunity by minerals, such as amorphous and crystalline silica, the main constituents of desert dust, which can act as damage-associated molecular patterns^{34,35}; or microorganism-derived, substances such as lipopolysaccharide or β -glucan, which can act as pathogen-associated molecular patterns¹⁰; and (3) provision of a surface on which air pollutants react with each other and produce chemicals, such as quinones, that induce oxidative stress in cells,³⁶ which can lead to the production of damage-associated molecular patterns and eventually activate innate immunity. We also found that various factors were effect modifiers of desert dust, including the coexistence of pollen in the air, IgE response to JCP, history of allergic rhinitis, and duration of time spent outside on dust days. The variability in results relative to previous studies may partly be attributed to these factors. A more complete understanding of these effect modifiers may help develop effective countermeasures.

The strengths of this study include the study design. Questionnaires were sent to mobile phones of participants on dust days. Thus, outcome data were collected while memories were fresh. This method ensured timely data acquisition of information regarding symptoms and behavior and contributed to the high accuracy of data.

This study has some limitations worth noting. First, symptoms were self-reported and not confirmed by medical professionals. In other words, symptoms were not distinguished by origin (eg, allergy, infection, other). Thus, our speculation regarding the adjuvant effects is solely based on the timing of symptoms and vulnerability of participants (eg, IgE to pollen). Moreover, reported symptoms may have been biased on heavy Asian dust days because of participant perceptions, although we never informed the participants if the day was an Asian dust day or not. However, it is noteworthy that the increase in risk of allergic symptoms was observed in association with a very low level of desert dust on control days, which would be free from perception bias. Another limitation relates to generalizability. We investigated pregnant

women, whose immune responses might have been altered due to pregnancy. Further studies should be performed to verify whether our findings also apply to the nonpregnant population. Finally, we only observed exacerbation of symptoms in those who were already sensitized to pollen. It remains unclear whether desert dust exerts adjuvant effects in primary immune responses (ie, whether it enhances sensitization in not-yet-sensitized individuals in real-life settings). This aspect is important from the public health perspective and should be investigated further.

In conclusion, ambient desert dust level was associated with an increased risk of allergic symptoms in pollen-sensitized pregnant women when pollen was present in the air. The increase in risk was dose dependent and was observed even at low levels of desert dust. These results support the hypothesis that desert dust exerts adjuvant effects in humans and raise a new perspective to consider for dust control in public health.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.02.002>.

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eMethods

Measurements

Serum samples were collected 3 times at each trimester during pregnancy for the Japan Environment & Children's Study (JECS), and IgE to common allergens was measured on the serum sampled in the first trimester. The local sulfur dioxide, nitric dioxide, and oxygen levels were obtained from 14 air-pollution monitoring stations, and climatic variables were obtained from 22 meteorologic stations in the study area. Pollen data were obtained from the Ministry of Environment of Japan (a total of 5 measurement sites) and the Japan Weather Association (a total of 3 measurement sites). The daily mean data at the closest station from the participant's residence was used for the exposure measurement on the day for each participant. Each pollutant was examined for association with outcomes using threshold models with various cutoff values (the standard threshold for air pollution in Japan and the 95th, 90th, 75th, and 50th percentiles of the observed distributions), and the best model was determined based on quasi-likelihood under the independence model criterion values. Factors associated with outcomes ($P < .10$) were used as possible confounders.

During the study period, light detection and ranging system (LIDAR) data were not available for a total of 97 days (8.9% of all eligible days); most of these days were isolated, but in other cases, data were missing for 2 straight days (13 cases) or 3 straight days (one case). For days with missing data, we adopted the mean of recorded levels on the day before and after,¹ on confirming the mean to be consistent with suspended particulate matter (SPM) or particulate matter 2.5 μm or less in diameter (PM2.5) values.

eResults

Lag Effects

eFigure 3a shows how the OR changes with an increasing lag time from day 0 (Asian dust day) to day 5 (5 days after an Asian dust day), with each lag fitted to the model one at a time. These different lag effects are not adjusted for each other. To address this, all the lagged variables (the 0- to 5-day shifted series) were simultaneously entered in the model (eFig 3b; distributed lag model). In comparison with the individual lag models, all the effect estimates

for lag days 0 to 5 inclusive have now moved toward the null, suggesting that the estimated individual lag effects were confounded by each other. Still, an increased risk was observed for several days, yielding a net effect of an OR of 1.23 (95% CI, 1.16–1.31) for 3 consecutive days and an OR of 1.26 (95% CI, 1.19–1.35) for a week (eFig 3b).

Comparison of the Effects of PM2.5 and SPM

PM2.5 and PM10 have long been monitored in investigations of the effects of PM on health outcomes. To deepen our understanding of PM effects, we analyzed PM2.5 and SPM (PM7) data using the same method. Similar to LIDAR data, exacerbation of allergic symptoms was observed at very low levels of PM2.5 and SPM and increased in a dose-dependent manner (eFig 4 and eFig 5). However, although LIDAR data did not reveal a clear increase in risk without pollen in the air, PM2.5 and SPM increased the risk in the absence of pollen, albeit with wide 95% confidence intervals (eFig 6 and eFig 7). Moreover, a greater influence was observed in participants with serum IgE antibodies to HDM, as well as those with allergic rhinitis or positive serum IgE result to Japanese cedar pollen testing (eFig 8 and eFig 9).

Sensitivity Analysis

We conducted a sensitivity analysis taking into consideration the effect of location and season, as well as a subpopulation analysis by location and season (eTable 7). Furthermore, for pollen data, we used pollen counts determined by the Durham method presented by the Japan Weather Association (eTable 8) instead of by the beta-ray attenuation method presented by the Ministry of the Environment.² We also conducted analysis excluding the data for which LIDAR's dust level was not consistent with the ground level (ie, LIDAR's desert dust day [$>0.07/\text{km}$] with SPM $<20 \mu\text{g}/\text{m}^3$ [a total of 6 days]) (eTable 9). These procedures did not substantially change the main results.

eReferences

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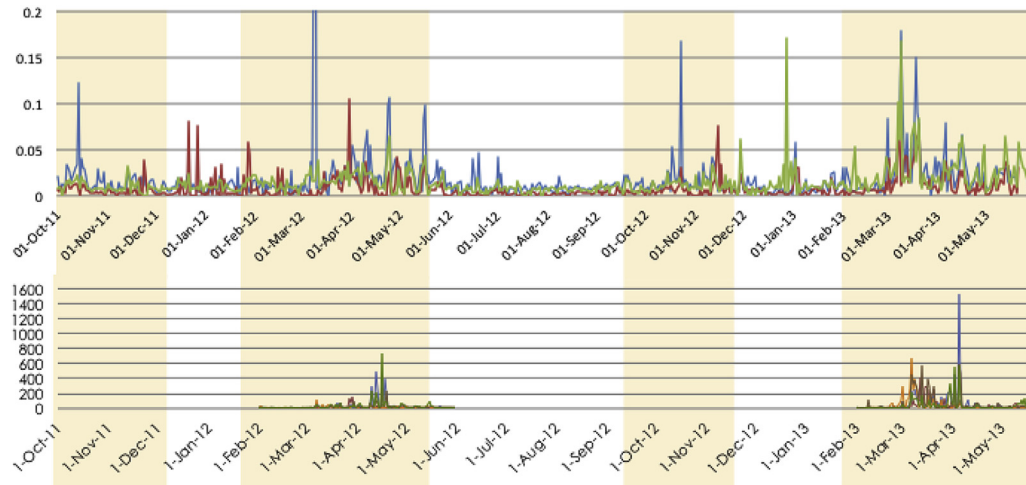
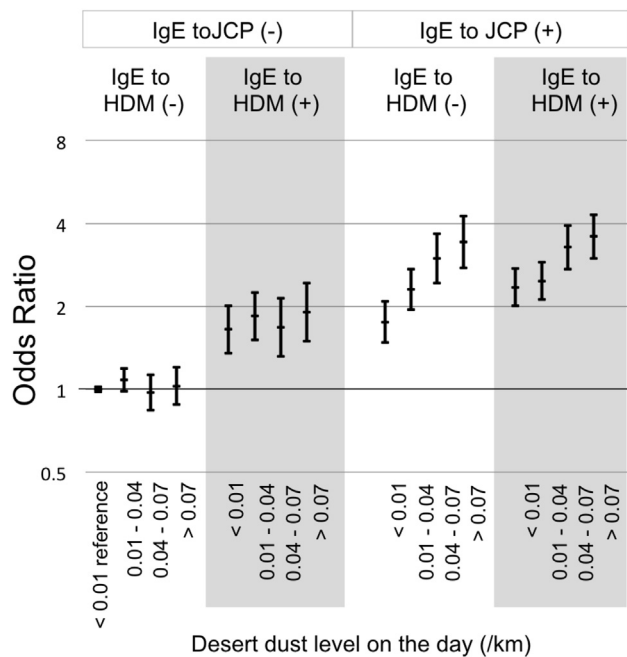


Figure 1. Time course of daily dust level in kilometers (upper) and pollen counts in cubic meters (lower) during the study period (shaded). For dust levels, blue indicates Kyoto (Higashi-Osaka); red, Toyama; and green, Tottori (Matsue). For pollen counts, blue indicates Kyoto (Kyoto City area); purple, Kyoto (Nagahama area); green, Kyoto (Kizugawa area); red, Toyama; and orange, Tottori.



n=2849, 3056, 811, 1147, 1367, 1407, 392, 579, 2177, 2480, 648, 964, 3562, 3755, 1059, 1479

Figure 2. Crude odds ratios and 95% confidence intervals for symptom development by desert dust level and serum IgE to Japanese cedar pollen (JCP) and house dust mite (HDM), relative to days with $<0.01/\text{km}$ desert dust (below the 50th percentile over the study period) in participants with negative IgE to HDM and JCP.

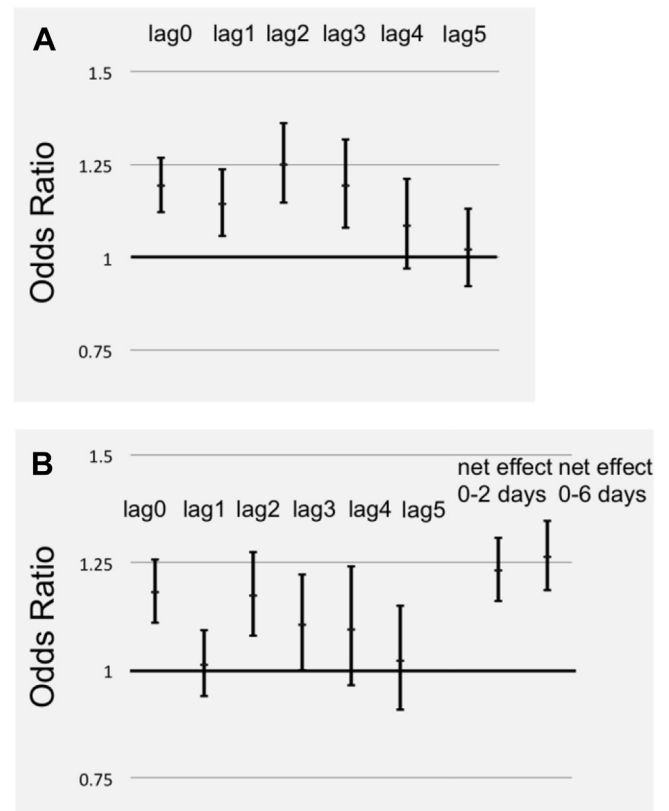


Figure 3. Odds ratios and 95% confidence intervals (error bars) for symptom development relative to days with less than $0.07/\text{km}$ desert dust. (A) Lag effects modeled one at a time. (B) Lag effects in the distributed lag model where lagged variables were simultaneously entered in a model and net effects where exposure was coded 1 if any previous 2 or 6 days had at least one Asian dust day, otherwise 0. Model was adjusted for nitric dioxide (threshold model with cutoff value of 15 ppb: 90th percentile), sulfur dioxide (with cutoff value of 3 ppb: 75th percentile), pollen (with cutoff value of $0/\text{m}^3$), and climatic variables (lowest temperature, temperature difference within the day, and humidity; all were treated as continuous variables).

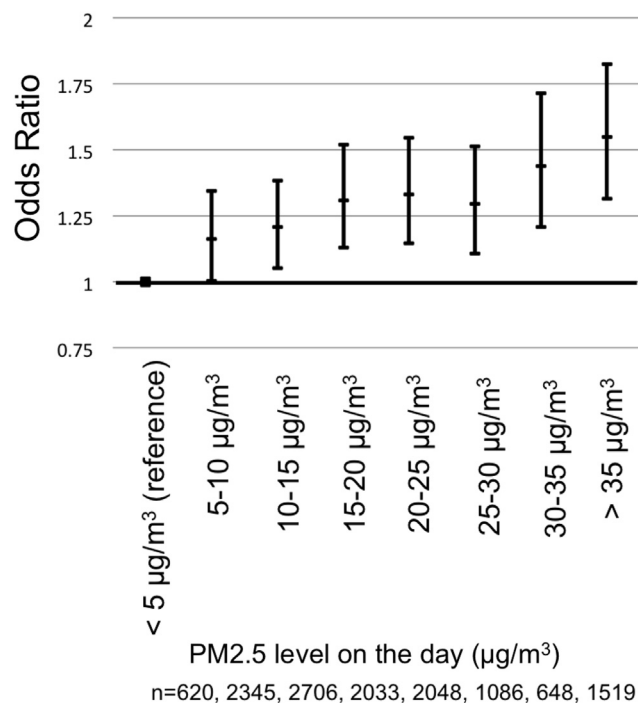


Figure 4. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by particulate matter 2.5 2.5 µm or less in diameter (PM_{2.5}) on the day relative to days with less than 5 µg/m³ of PM_{2.5}.

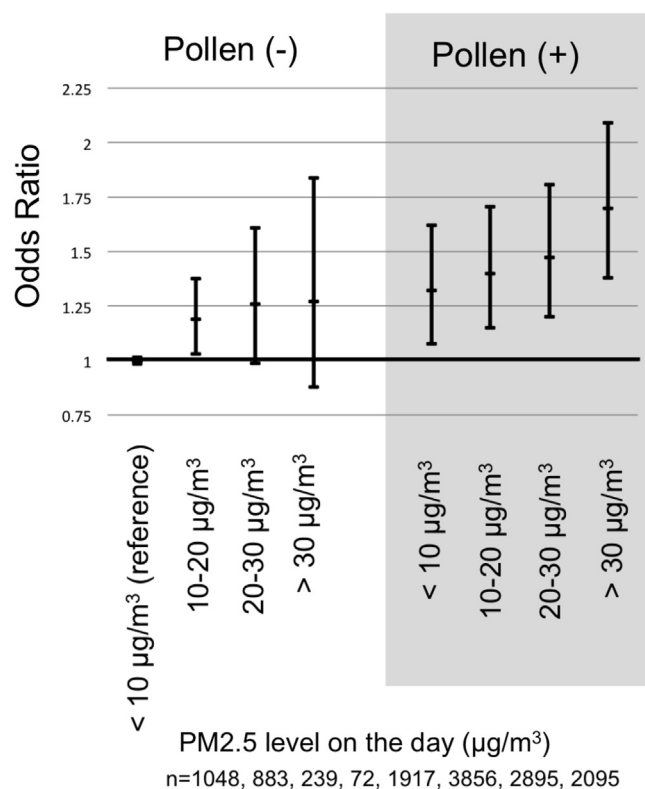


Figure 6. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by particulate matter 2.5 2.5 µm or less in diameter (PM_{2.5}) on the day and presence of ambient cedar or cypress pollen relative to days with less than 5 µg/m³ of PM_{2.5} without ambient pollen. Minus sign indicates negative; plus sign, positive.

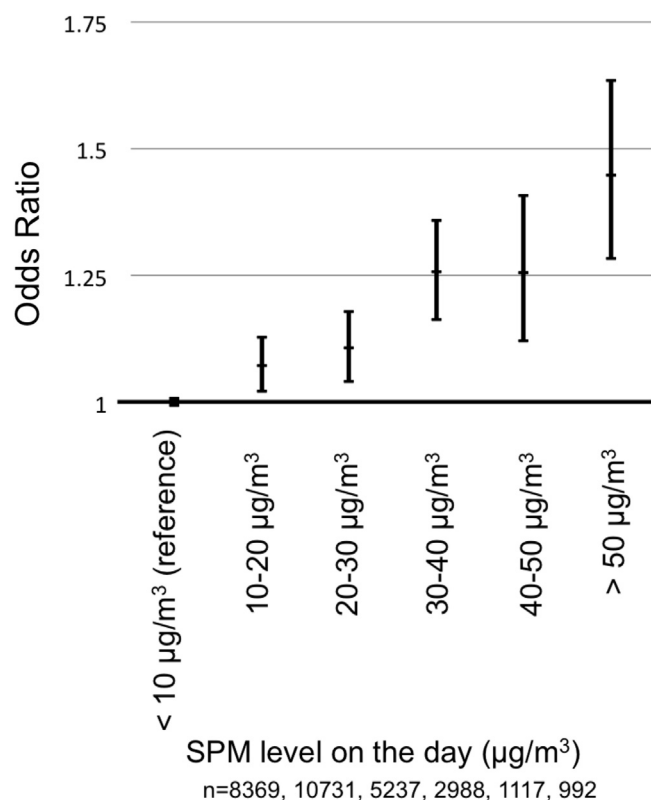
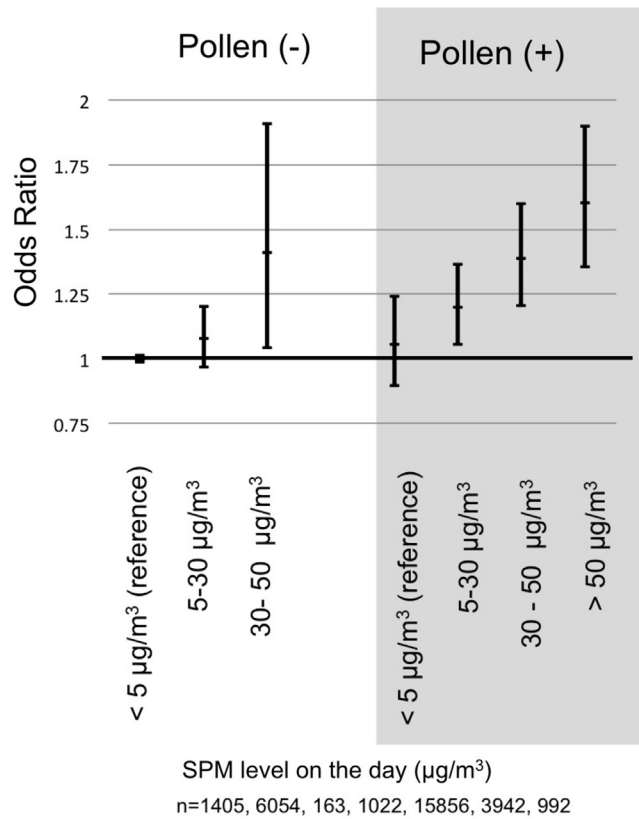
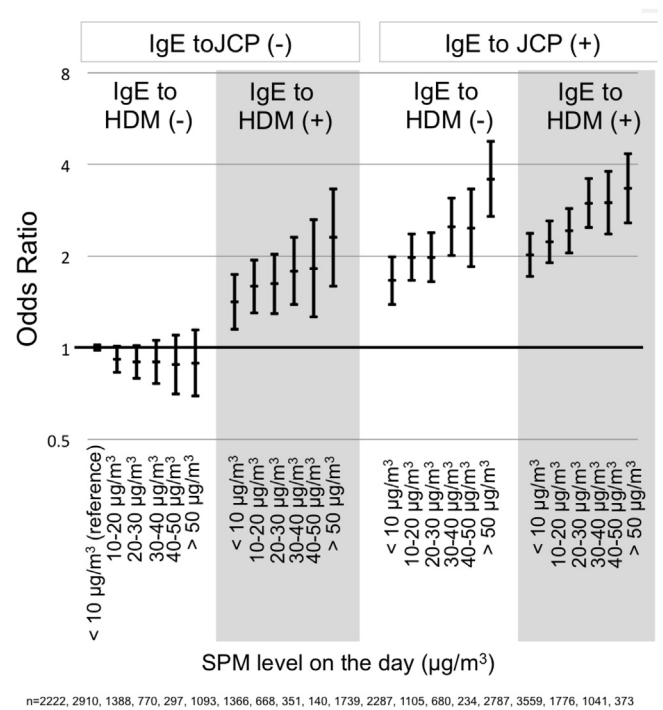


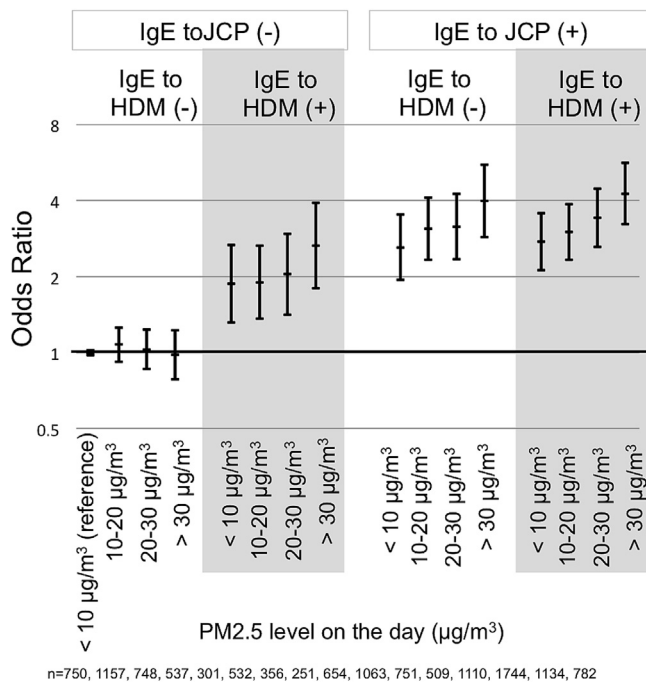
Figure 5. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by suspended particulate matter (SPM) level on the day relative to days with less than 10 µg/m³ of SPM.



eFigure 7. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by suspended particulate matter (SPM) level on the day and presence of ambient cedar or cypress pollen relative to days with less than 10 $\mu\text{g}/\text{m}^3$ of SPM without ambient pollen. Minus sign indicates negative; plus sign, positive.



eFigure 9. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by suspended particulate matter (SPM) level on the day and serum IgE responses to Japanese cedar pollen (JCP) and house dust mite (HDM) relative to days with less than 10 $\mu\text{g}/\text{m}^3$ of SPM in participants with negative IgE test results to HDM and JCP. Minus sign indicates negative; plus sign, positive.



eFigure 8. Crude odds ratios and 95% confidence intervals (error bars) for symptom development by particulate matter 2.5 μm or less in diameter (PM_{2.5}) level on the day and serum IgE to Japanese cedar pollen (JCP) and house dust mite (HDM) relative to days with less than 5 $\mu\text{g}/\text{m}^3$ of PM_{2.5} in participants with negative IgE test results to HDM and JCP. Minus sign indicates negative; plus sign, positive.

eTable 1

Characteristics of Participants Who Answered the Questionnaire at Least Once

Characteristic	Kyoto (n = 1,100)	Toyama (n = 1,477)	Tottori (n = 750)
Age, mean (SD), y ^a	32.2 (4.5)	31.0 (4.8)	30.9 (4.8)
Height, mean (SD), cm ^a	158.7 (5.2)	158.8 (5.3)	157.9 (5.4)
BMI before pregnancy, mean (SD) ^a	20.6 (2.8)	20.9 (2.8)	20.8 (3.1)
History of allergic diseases, No. (%)			
Asthma	114 (10.4)	152 (10.3)	99 (13.2)
Allergic rhinitis	504 (45.8)	564 (38.2)	290 (38.7)
Atopic dermatitis	202 (18.4)	228 (15.4)	148 (19.7)
Serum positive IgE result, No. (%)			
Japanese cedar pollen positive	662 (60.2)	744 (50.4)	359 (47.9)
House dust mite positive	521 (47.4)	668 (45.2)	313 (41.7)
Sample not available	66 (6.0)	128 (8.7)	50 (6.7)
Smoking history, No. (%) ^a			
Never smoked	714 (64.9)	896 (60.7)	476 (63.5)
Stopped before pregnancy	259 (23.5)	367 (24.8)	172 (22.9)
Stopped after pregnancy	77 (7.0)	131 (8.9)	67 (8.9)
Current smoker	23 (2.1)	35 (2.4)	19 (2.5)
Blank ^b	27 (2.5)	48 (3.2)	16 (2.1)
Educational level, No. (%) ^a			
Junior high school	20 (1.8)	44 (3.0)	31 (4.1)
High school	176 (16.0)	340 (23.0)	230 (30.7)
Vocational school	185 (16.8)	338 (22.9)	178 (23.7)
College (2 years)	256 (23.3)	258 (17.5)	118 (15.7)
High vocational school	8 (0.7)	17 (1.2)	25 (3.3)
College (4 years)	373 (33.9)	382 (25.9)	142 (18.9)
Graduate school	61 (5.5)	26 (1.8)	11 (1.5)
Blank ^b	21 (1.9)	72 (4.9)	15 (2.0)
Family income per year, No. (%) ^a			
<\$20,000	39 (3.5)	34 (2.3)	39 (5.2)
\$20,000–40,000	299 (27.2)	279 (25.7)	258 (34.4)
\$40,000–60,000	352 (32.0)	492 (33.3)	221 (29.5)
\$60,000–80,000	184 (16.7)	250 (16.9)	108 (14.4)
\$80,000–100,000	86 (7.8)	111 (7.5)	35 (4.7)
>\$100,000	83 (7.5)	67 (4.6)	27 (3.6)
Blank ^b	57 (5.2)	144 (9.7)	81 (8.3)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^aRefers to Japan Environment & Children's Study (tentative data).^bBlank includes those who did not return the answer sheet.**eTable 2**

Residential Environment of Participants

Environment	Kyoto (n = 1,100)	Toyama (n = 1,477)	Tottori (n = 750)
Housing type, No. (%)			
Wooden detached house	568 (51.6)	758 (51.3)	341 (45.5)
Steel or SRC detached house	87 (7.9)	91 (6.2)	23 (5.7)
Wooden apartment	59 (5.4)	147 (10.0)	84 (11.2)
SRC apartment	363 (33.0)	402 (27.2)	260 (34.7)
Others	4 (0.4)	6 (0.4)	6 (0.8)
Blank ^a	19 (1.7)	73 (4.9)	16 (2.1)
Building age, mean (SD), y ^b	3.4 (1.7)	3.3 (1.7)	3.7 (1.7)
Pet owning, No. (%) ^b			
Yes	215 (19.5)	240 (16.2)	173 (23.1)
No	865 (78.6)	1,166 (78.9)	561 (74.8)
Blank ^a	20 (1.8)	71 (4.8)	16 (2.1)
Molds in the residence, No. (%) ^a			
Yes	693 (63.0)	862 (58.4)	502 (66.9)
No	381 (34.6)	542 (36.7)	231 (30.8)
Blank ^b	26 (2.4)	73 (4.9)	17 (2.3)
Use of air purifiers, No. (%) ^a			
Yes	560 (50.9)	649 (43.9)	309 (41.2)
No	523 (47.5)	756 (51.2)	427 (56.9)
Blank ^b	17 (1.5)	72 (4.9)	14 (1.9)
No. of people in the house, mean (SD)	3.2 (1.2)	3.4 (1.5)	3.5 (1.5)
Use of dirty heaters, No. (%) ^a			
Yes	597 (54.3)	839 (56.8)	474 (63.2)
No	400 (36.4)	561 (38.0)	255 (34.0)
Blank ^b	103 (9.4)	77 (5.2)	21 (2.8)
Distance from main road, No. (%)			
<30 m	262 (23.8)	337 (22.8)	169 (22.5)
30–50 m	181 (16.5)	232 (15.7)	124 (16.5)
>50 m	483 (43.9)	630 (42.7)	291 (38.8)
Blank ^b	174 (15.8)	278 (18.8)	166 (22.1)

Abbreviation: SRC, steel reinforced concrete.

^aRefers to Japan Environment & Children's Study (tentative data).^bBlank includes those who did not return the answer sheet.

eTable 3Air Pollution and Climatic Factors on Asian Dust Days and Control Days According to LIDAR Measurements at 135-m Altitude in 3 Regions^a

Factor	Asian Dust Days (n = 27)				Control Days (n = 1,062)			
	Median	Maximum	75th Percentile	25th Percentile	Median	Maximum	75th Percentile	25th Percentile
Air pollution								
Nonspherical PM, /km	0.090	0.498	0.107	0.078	0.012	0.070	0.021	0.006
Spherical PM, /km	0.094	0.340	0.194	0.038	0.062	0.567	0.106	0.034
SPM, $\mu\text{g}/\text{m}^3$	34.2	75.5	39.8	20.8	11.6	54	18	7.4
PM2.5, $\mu\text{g}/\text{m}^3$ (n = 21,581) ^b	27.6	49.6	33.8	20.3	11.8	64	17	8.0
Sulfur dioxide, ppm	4	7.96	5.75	2.71	0.62	7.75	3.17	0
Nitric dioxide, ppm	10.3	24.3	14.4	7.6	7.3	29	10.2	5.4
Oxygen, ppm	36.3	62.5	47.7	25.5	35	62.5	42.8	27
Pollen, /m ³	63.8	664.5	174.8	15.6	3	1514	12.9	0
Climatic factors								
Temperature, °C	14.7	24.2	18.8	11.6	12.5	24.5	17.3	7.5
Temperature difference from the previous day, °C	0.10	4.9	2.3	−1.5	0.15	7.9	1.6	−1.5
Temperature difference within the day, °C	12.6	17.6	14.7	8.3	8.8	21.6	11.4	6.5
Air pressure, hPa	1007	1016	1010	1004	1014	1028	1019	1010
Air pressure difference from the previous day, hPa	−2.9	10.3	1.4	−7.6	0.5	21.8	3.5	−2.9
Humidity, %	68	89	78	53	69	98	78	61

Abbreviations: LIDAR, light detection and ranging system; PM, particulate matter; PM2.5, particular matter 2.5 μm or less in diameter; SPM, suspended particulate matter.^aThere were 363 observations for each region, and accordingly the joined data had 363×3 observations in total.^bThe PM2.5 data are from Kyoto (n = 363) and Toyama (n = 239).**eTable 4**Correlation Coefficients Between Nonspherical Particulate Matter and Other Air Pollutants and Climatic Variables in 3 Regions^a

Variable	Correlation Coefficient (95% CI)
Spherical PM	0.267 (0.211 to 0.321)
Nitric dioxide	0.022 (−0.037 to 0.082)
Sulfur dioxide	0.420 (0.369 to 0.467)
Oxygen	0.364 (0.196 to 0.384)
Pollen	0.433 (0.384 to 0.480)
Humidity	−0.415 (−0.365 to −0.463)
Air pressure	−0.227 (−0.170 to −0.283)
Air pressure difference from the previous day	−0.001 (0.059 to −0.060)
Temperature	0.175 (0.117 to 0.232)
Temperature difference within the day	0.341 (0.287 to 0.392)
Temperature difference from the previous day	0.130 (0.071 to 0.188)

Abbreviation: CI, confidence interval.

^aThe Spearman rank correlation was used. There were 363 pairs for each region, and accordingly the joined data had 363×3 pairs, and correlations on the whole data are shown.**eTable 5**

Distribution of Symptom Score

Variable	Mean (SD)	Median	25th Percentile	75th Percentile	Maximum
Total symptom score					
Asian dust days (n = 4,374)	2.48 (3.8)	1	0	3	30
Control days (n = 25,060)	1.60 (2.8)	0	0	2	30
All days (n = 29,434)	1.73 (2.9)	0	0	2	30
Nose score					
Asian dust days	1.66 (2.5)	0	0	2	12
Control days	1.13 (2.0)	0	0	2	12
All days	1.21 (2.0)	0	0	2	12
Eye score					
Asian dust days	0.59 (1.3)	0	0	1	9
Control days	0.28 (0.8)	0	0	0	9
All days	0.33 (0.9)	0	0	0	9
Chest score					
Asian dust days	0.25 (0.8)	0	0	0	9
Control days	0.23 (0.8)	0	0	0	9
All days	0.23 (0.8)	0	0	0	9

eTable 6

β Estimation (95% CI) With the Consideration of Interaction With the History of Allergic Rhinitis and the Participants' Serum IgE Test Results^a

	Estimate (95% CI)	P Value
History of allergic rhinitis		
Desert dust ^b	0.098 (0.047 to 0.148)	<.001
Allergic rhinitis	1.148 (0.954 to 1.342)	<.001
Interaction term	0.114 (0.035 to 0.193)	.005
JCP		
Desert dust ^b	0.009 (–0.048 to 0.067)	.75
IgE to JCP ^c	1.084 (0.890 to 1.278)	<.001
Interaction term	0.230 (0.152 to 0.307)	<.001
HDM		
Desert dust ^b	0.129 (0.074 to 0.185)	<.001
IgE to HDM ^d	0.500 (0.306 to 0.694)	<.001
Interaction term	0.026 (–0.052 to 0.104)	.52

Abbreviations: CI, confidence interval; HDM, house dust mite; JCP, Japanese cedar pollen.

^aModel was adjusted for smoking status of participants, smoking status of participants' partners, house incomes, age, and body mass index.

^bDesert dust was log transformed with the addition of 0.0001 to the 0 value.

^cIgE response to JCP was treated as categorical (negative or positive).

^dIgE to HDM was treated as categorical (negative or positive).

Adjusted by smoking status of subjects, smoking status of subjects' partners, house incomes, age, and BMI.

eTable 8

β Estimation (95% CI) Adjusted for Other Pollutants and Climatic Variables, Treating Desert Dust and Cedar or Cypress Pollen (Durham Data) As Numerical After Log Transformation^a

Variable	β Estimate (95% CI)	P Value
Desert dust ^b	–0.019 (–0.075 to 0.037)	.50
Cedar or cypress pollen (Durham data) ^b	0.225 (0.131 to 0.319)	<.001
Interaction term of desert dust and pollen ^b	0.048 (–0.003 to 0.100)	.007
Sulfur dioxide (>3 ppb) ^b	0.099 (0.002 to 0.196)	.046
Lowest temperature on the day ^b	–0.007 (–0.016 to 0.001)	.07
Temperature difference within the day ^b	0.003 (–0.005 to 0.011)	.44
Humidity on the previous day ^b	–0.044 (–0.007 to –0.002)	.001

Abbreviation: CI, confidence interval.

^aModel adjusted for smoking status of participants, smoking status of participants' partners, house incomes, age, and body mass index.

^bSulfur dioxide was treated as dichotomous (with cutoff value of 3 ppb). Climatic variables were treated as numerical. Desert dust and cedar or cypress pollen (Durham data) were treated as numerical after log transformation, with the addition of 0.0001 and 0.5 for 0 value for each.

eTable 7

ORs (95% CIs) for Any Allergic Symptom Development and Adjusted for Other Pollutants, Climatic Variables, Locations (3 Sites), and Seasons (2 Seasons)^a

Variable	OR (95% CI)	P Value
With interaction terms		
Desert dust (>0.07/km) ^b	1.10 (1.03–1.17)	.003
Toyama ^c	0.80 (0.70–0.91)	.001
Tottori ^c	0.96 (0.82–1.12)	.570
Season (autumn) ^d	0.99 (0.88–1.11)	.850
Sulfur dioxide (>3 ppb) ^b	1.14 (1.05–1.24)	.003
Cedar or cypress pollen (>40/m ³) ^b	1.37 (1.28–1.47)	<.001
Lowest temperature on the day ^b	0.99 (0.98–0.99)	<.001
Temperature difference within the day ^b	1.01 (1.00–1.01)	.008
Humidity on the previous day ^b	1.00 (0.99–1.00)	<.001
Without interaction terms		
Desert dust (>0.07/km) ^b	1.15 (1.05–1.25)	.002
Toyama ^c	0.81 (0.71–0.92)	.002
Tottori ^c	0.96 (0.82–1.13)	.640
Season (autumn) ^d	0.99 (0.88–1.11)	.882
Interaction term of desert dust and Toyama	0.87 (0.74–1.01)	.069
Interaction term of desert dust and Tottori	0.95 (0.78–1.17)	.649
Interaction term of desert dust and season	0.97 (0.76–1.24)	.810
Sulfur dioxide (>3 ppb) ^b	1.14 (1.04–1.24)	.003
Cedar or cypress pollen (>40/m ³) ^b	1.36 (1.27–1.47)	<.001
Lowest temperature on the day ^b	0.99 (0.98–0.99)	<.001
Temperature difference within the day ^b	1.01 (1.00–1.01)	.004
Humidity on the previous day ^b	1.00 (0.99–1.00)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

^aModel was adjusted for smoking status of participants, smoking status of participants' partners, house incomes, age, and body mass index.

^bDesert dust, sulfur dioxide, and cedar or cypress pollen were treated as dichotomous (with cutoff values of 0.07/km, 3 ppb, and 40/m³, respectively). Climatic variables were treated as numerical.

^cComparison with Kyoto.

^dComparison with spring.

eTable 9

OR (95% CI) for Any Allergic Symptom Development in an Adjusted Model Excluding Days With LIDAR's Desert Dust Day (>0.07/km) and SPM Under 20 $\mu\text{g}/\text{m}^3$ (Total of 6 Days)^a

Variable	OR (95% CI)	P Value
Desert dust (>0.07/km) ^b	1.12 (1.04–1.21)	.003
Sulfur dioxide (>3 ppb) ^b	1.17 (1.08–1.27)	<.001
Cedar or cypress pollen (>40/m ³) ^b	1.37 (1.28–1.48)	<.001
Lowest temperature of the day ^c	0.99 (0.98–0.99)	<.001
Temperature difference during the day ^c	1.01 (1.00–1.01)	.01
Humidity on the previous day ^c	1.00 (0.99–1.00)	<.001

Abbreviations: CI, confidence interval; LIDAR, light detection and ranging system; OR, odds ratio.

^aModel was adjusted for smoking status of participants, smoking status of participants' partners, house incomes, age, and body mass index.

^bDesert dust, sulfur dioxide, and cedar or cypress pollen were treated as dichotomous (with cutoff values of 0.07/km, 3 ppb, and 40/m³, respectively).

^cClimatic variables were treated as numerical.