

DR. TOSHIKO ITAZAWA (Orcid ID : 0000-0002-7055-3722)

DR. KEI HAMAZAKI (Orcid ID : 0000-0003-0456-6805)

Article type : Original Article: Epidemiology and Genetics

Title

The impact of exposure to desert dust on infants' symptoms and countermeasures to reduce the effects

Toshiko Itazawa, MD, PhD ¹, Kumiko T Kanatani, MD, MAS ², Kei Hamazaki, MD, PhD ³, Hidekuni Inadera, MD, PhD ³, Akiko Tsuchida, MS ³, Tomomi Tanaka, MD, PhD ¹, Takeo Nakayama, MD, PhD ⁴, Tohshin Go, MD, PhD ², Kazunari Onishi, MS, PhD ^{5,6}, Yoichi Kurozawa, MD, PhD ⁶, Yuichi Adachi, MD, PhD ¹, Japan Environment and Children's Study Group

¹ University of Toyama, School of Medicine, Department of Pediatrics, ² Kyoto University Graduate School of Medicine, Japan Environment and Children's Study Kyoto Regional Center, ³ University of Toyama, School of Medicine, Department of Public Health, ⁴ Kyoto University School of Public Health, Department of Health Informatics, ⁵ Division of Environmental Health, Graduate

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14166](https://doi.org/10.1111/ALL.14166)

This article is protected by copyright. All rights reserved

School of Public Health, St.Luke's International University, ⁶ Division of Health
Administration and Promotion, Faculty of Medicine, Tottori University

Contact information for corresponding authors and requests for reprints

Yuichi Adachi, MD, PhD

University of Toyama Graduate School of Medicine, Department of Pediatrics

Sugitani 2630, Toyama-shi, Toyama, 930-0194, Japan

+81-76-434-7313 (tel)

+81-76-434-5029 (fax)

mail: yadachi@med.u-toyama.ac.jp

Short title

The impact of exposure to desert dust on infants' symptoms

Sources of support: This work was supported by the Environment Research and Technology Development Fund from the Ministry of the Environment, Japan [5-1555(2015-2017)] and the Environmental Restoration and Conservation Agency, Japan (2014-2016), and was conducted as an adjunct study to the Japan Environment and Children Study (JECS). The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Japanese government.

Contributions: KTK and YA designed the study, TI, KTK, KH, HI, TN, TG, KO, YK, and YA contributed to the grant acquisition, and KTK and KH analyzed the data. TI, KTK, YA, KH, HI, TT, TG and TN interpreted the data. TI and KTK drafted the work. TN, YA, HI, and TT gave academic feedback. HI, KH, AT, TT and YA managed the JECS in Toyama, KTK, TG and TN in Kyoto, and KO and YK in Tottori. All authors contributed to the interpretation of the results. All authors reviewed the final manuscript. All authors gave their final approval of the submitted manuscript and agreed to be accountable for all aspects of the work.

Abstract

Background

The association between particulate matter (PM), including desert dust, and allergic symptoms has not been well studied. We examined whether PM exacerbated nose/eye/respiratory symptoms in infants, with a focus on the desert dust element, and assessed possible countermeasures.

Methods

We conducted a panel study of 1,492 infants from October 2014 to July 2016 in 3 regions in Japan as an adjunct study of the Japan Environment and Children's Study. Infants' daily symptom scores and behaviors were acquired by web-based questionnaires sent to mothers, who answered within a day using mobile phones. Odds ratios (OR) for symptom development per increased fine PM or desert dust exposure were estimated. Regular use of medications and behaviors on the day of exposure were investigated as possible effect modifiers.

Results

Infants developed nose/eye/respiratory symptoms significantly more often in accordance with fine particulate levels (adjusted OR per $10\mu\text{g}/\text{m}^3$ increase: 1.04, 95% confidence interval [CI]: 1.01-1.07). A model including both fine particulates and desert dust showed reduced OR for fine particulates and robust OR for desert dust (adjusted OR per $0.1/\text{km}$ increase: 1.16, 95% CI: 1.09-1.23). An increased OR was observed both in infants who had previously wheezed and in those who had never wheezed. Receiving information on the particulate forecast, reducing time outdoors, closing windows, and regular use of leukotriene receptor antagonists were significant effect modifiers.

Conclusions

Trans-border desert dust arrival increased the risk of nose/eye/respiratory symptoms development in infants. Regular use of leukotriene receptor antagonists and other countermeasures reduced the risk.

Key words

Allergy Control Score, Asian dust, Japan Environment and Children's Study (JECS), leukotriene receptor antagonists (LTRA), particulate matter (PM)_{2.5}

Abbreviations

OR: odds ratio

95% CI: 95% confidence interval

PM: particulate matter

LIDAR: light detection and ranging

SO₂: sulfur dioxide

NO₂: nitrogen dioxide

Ox: photochemical oxidants

ISAAC: International Study of Asthma and Allergies in Childhood

GEE: generalized estimating equation

LTRA: leukotriene receptor antagonist

RCT: randomized controlled trial

Introduction

The increase in incidence of allergic diseases has become an important health issue.(1, 2) Environmental pollution, such as air pollutants and chemical substances, is thought to be an important factor in the increase and worsening of allergic diseases.(3-6) One major air pollutant, particulate matter (PM), has been shown to be associated with mortality and morbidity from cardiovascular and respiratory diseases.(7-9) A causal relationship is considered “likely” between short-term exposure to fine particulate matter (PM_{2.5}; particulate matter ≤2.5 µm in aerodynamic diameter) and respiratory effects.(10-12) Particulate matter is the generic term for a broad class of substances that are diverse chemically, physically, and in size, thus complicating the assessment of associated health effects.(12)

Desert dust dominates PM over some continental regions, with relatively higher concentrations especially in urban South Asia and China, accounting for about 35% of PM with diameter smaller than 10 µm. Half of that dust is from the Sahara in Africa, and 20% is from the Asian continent and is referred to as Asian dust.(13) Sahara dust is transported to the Mediterranean and Europe, and across the Atlantic to the Americas. Some epidemiological studies have suggested that Sahara dust increases mortality and both respiratory and cardiovascular morbidity, and exacerbates asthma.(14-18) Similarly, it has been reported that Asian dust events are associated with an increased risk of mortality,(19-23) cardiovascular disease,(24-26) respiratory disease,(27-31) allergic symptoms,(32, 33), and conjunctivitis.(34, 35)

We previously reported the adjuvant-like effects of desert dust in

124 pollen-sensitized pregnant women, in whom an elevated risk of allergic
125 symptoms was observed at low levels of desert dust.(32) However, several
126 facets of desert dust exposure remain unknown, such as the effects on allergic
127 symptoms in infants, which populations are vulnerable and susceptible, and how
128 the effects can be reduced. This information would be particularly important for
129 future public health because growing evidence suggests that the major 3 factors
130 affecting desert dust activities – desertification, climatic variability, and global
131 warming – can increase dust formation.(36-38) Accordingly, we investigated the
132 effects of PM_{2.5} and desert dust on nose/eye/respiratory symptoms in
133 infants who had or had not wheezed previously, and estimated the impact of
134 possible preventive measures that are now conventionally implemented against
135 air pollution, such as avoiding being outdoors and closing windows.

Materials and Methods

Study design

This longitudinal study was initiated in 2014 to examine the effects of desert dust and PM_{2.5} exposure on nose, eye, and respiratory symptoms in infants in Kyoto, Toyama, and Tottori. The study protocol was approved by the Japan Environment and Children's Study (JECS) and ethics committees of Kyoto University, University of Toyama, and Tottori University.

Upon enrollment, baseline information such as history of asthma, attendance in group-care, and mother's working style was collected via a web-based questionnaire sent to mobile phones.(39) Various lifestyle and body parameters including housing environment, body weight at birth, and mother's body weight changes and smoking habits during pregnancy were obtained during the JECS. Details of these parameters are described elsewhere.(40-42)

In the evening, when high desert dust (Asian dust days; >0.07/km on 12 hour-average measured by light detection and ranging; LIDAR) or high PM_{2.5} (>35µg/m³ on 12 hour-average) was observed, all mothers in that study area received a self-administered questionnaire about their children's symptoms and behaviors during the day via their mobile phones. For comparison, an identical questionnaire was sent on other days to selected mothers, with each mother having an approximately 10% probability on those days to receive the questionnaire.(39) In effect, each mother randomly received an identical questionnaire once every 10 days during the study period, in addition to on the polluted days (Asian dust days and high PM_{2.5} days). Mothers were not informed if the day was or was not a polluted day.(39)

Participants and setting

The JECS is an on-going birth cohort study that began in 2011 and evaluates the impact of various environmental factors on children's health and development. A total of 100,000 children and their parents take part across 15 regions in Japan,(40-42) with follow-up programs to examine health periodically from the early stages of pregnancy until the participating child reaches 13 years of age. The JECS allows for adjunct studies that pertain to the main study. 'Effects of desert dust exposure on children's health' is our adjunct study involving 3 JECS Regional Centres in Kyoto, Toyama, and Tottori. These areas are located in Western Japan, with Kyoto in a basin and Toyama and Tottori facing the Sea of Japan (Figure E1). Each has urban, suburban, and rural areas.

JECS participants in the 3 regions who also agreed to participate in the adjunct study 'Effects of desert dust exposure on children's health' were enrolled before the birth of their children. More than half of the JECS participants in the target regions agreed to participate in the adjunct study. All participants provided written informed consent, and they were again electronically asked if they consented to participate in each part of the study (pregnant part, infant part, and randomized controlled trial [RCT] part) just before it began. This study was conducted as the second part (infant part) of 'Effects of desert dust exposure on children's health'. The JECS participants who fulfilled all of the following definitions were enrolled in this infant part of the adjunct study: 1) provided written informed consent to participate in this adjunct study at the initiation of the adjunct study during pregnancy; 2) were confirmed to use smartphones; and 3)

provided electronic consent to participate in the second part of the adjunct study (after childbirth).

The study started in October 2014, when participants were categorized as wheezers or non-wheezers according to how they responded to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire:(43) “Has your child ever had wheezing or whistling in the chest at any time in the past?” First, the wheezers were invited in October 2014, and additional participants including non-wheezers were invited in October 2015; the study continued to July 2016. Some non-wheezers at the start of the study experienced wheezing during the study, and their symptom responses after wheezing was experienced were analyzed as part of the wheezers group (Figure E2).

Exposure measures

To assess exposure to desert dust during the study period, we used LIDAR data obtained from each area (Higashi-Osaka LIDAR for Kyoto, Toyama LIDAR for Toyama, and Matsue LIDAR for Tottori). LIDAR is an optical remote sensing technology that measures scattered light to recognize shape differences of particles, and can distinguish desert dust (having rough surface) from other air pollutants, which are generally spherical.(21, 27, 32, 39, 42) Extinction coefficients measured by the LIDAR system at 135 m from the ground were compiled as 12-hour (06:00-18:00) average data.

Concentrations of PM_{2.5} and other air pollutants (sulfur dioxide [SO₂], nitrogen dioxide [NO₂], and photochemical oxidants [Ox]) were collected from 5 air-pollution monitoring stations in the target areas. Daily average concentrations

of PM_{2.5}, SO₂ and NO₂, and 8-hour (9 am-5 pm) average concentrations of Ox on each day were calculated from hourly concentrations measured at each station. Daily temperature, air pressure, and relative humidity data were obtained from 5 local observatories of the Japanese meteorological agency in the target areas.

Main outcome measures

The main outcome was the proportion of participants with any symptom (symptom score >0) as assessed by a self-administered questionnaire sent to mothers via mobile phone. The questionnaire included items from the Japanese version of the Allergy Control Score™, (39, 44, 45) which asked about daily nasal (sneezing, itching, running, and blockage), ocular (itching, tear flow, and redness), and bronchial (cough, wheezing, and dyspnea) symptoms on a 4-point scale (absent, mild, moderate, or severe).

Statistical analysis

The primary analysis was the association between proportion of subjects with any symptom (symptom score above 0) and a 10 µg/m³ increase in PM_{2.5} or a 0.1/km increase in desert dust, which is about 100µg/m³ of total suspended matter. The secondary outcomes were unplanned clinic visits and absence from day-care. The generalized estimating equation (GEE) was used to adjust intra-individual correlations. For analyses to examine possible confounders, the following factors were examined: local pollen level, local SO₂, NO₂, and Ox levels, local spherical particulate level (particulates other than desert dust), and

local meteorological variables (air pressure and its change from the previous day, average temperature and its change from the previous day, lowest temperature, and humidity).

Because the effects of desert dust and $PM_{2.5}$ can persist over several days, we examined the effects according to several lag times: on the day (lag 0) to a week after (lag 6) by single lag models.

To investigate possible effect modifiers, the following were examined: age, gender, number of siblings, socioeconomic status (family income, mother's education level), smoking in the house, if the mother got any information about particulates on the day, how long the child was outdoors on the day, if windows were open on the day, if futon and clothes were dried outside, and if air purifier was used on the day.

In addition, we conducted sensitivity analyses with a model of the log score for outcome and a model where missing data regarding desert dust and $PM_{2.5}$ were substituted by the average values of other regions on the day of reported symptoms.

All analyses were performed with SAS version 9.3 (SAS Institute Inc, North Carolina, USA).

Results

Participant characteristics

A total of 12,165 pregnant women had enrolled at JECS regional centers in Kyoto, Toyama, and Tottori by the end of August 2014. Of these, 5,803 (47.7%) provided consent to participate in the adjunct study during their pregnancies, and 4,703 of their children were registered after birth. Among these children, 2,759 were selected from those whose mothers used smartphones. Initially, 796 children who were confirmed to have wheezed at least once were invited to the study in October 2014, of which 515 were consented to participate. Another 1,963 children were invited to the study in October 2015, of which 973 were consented to participate. Both groups were followed until July 2016 (Figure E2).

A total of 86,839 questionnaires were sent on the evenings of polluted days and on other days, to which responses were received for 69,279 (79.8%) within the set time limit of 28 hours from date of issue. Of these, 69,001 (99.6%) responses contained complete answers for symptom scores.

Most participants were 1-3 years of age at entry (Table 1). Boys were dominant among wheezers while girls were dominant among non-wheezers, which is consistent with the general perception that boys wheeze more often than girls in that age range. Twenty-two percent of wheezers reported a physician's diagnosis of asthma, and about half of all wheezers started wheezing before 6 months of age.

PM_{2.5} and desert dust during the study period

The time courses of PM_{2.5} and desert dust levels in each area during the study

period are shown in Figure E3. The time courses were similar among the 3 locations, where the distance between locations is relatively short, 200-400 km. Timing of some PM_{2.5} peaks corresponded to that of desert dust, while other peaks, especially in August, were not explained by desert dust levels. The median levels of PM_{2.5} and desert dust were about 10 µg/m³ and 0.01/km, respectively (Table E1), and no “PM_{2.5} warning” by government was issued during the study period (Japanese government alerts the people when PM_{2.5} is expected to go above 70 µg/m³, and no such alert-system for desert dust is currently enforced in Japan). The correlations of PM_{2.5} and desert dust with other pollutants were weak (NO₂) or moderate (SO₂, O_x), and were not considered to produce multicollinearity problems (Table E2).

Nose, eye, and respiratory symptoms

The occurrence of any symptom (symptom score >0) was reported in 64.4% (17,257/26,778) of responses by those who had ever wheezed before study entry, 54.7% (23,103/42,223) of responses by those who had never wheezed before the response, and 58.5% (40,360/69,001) of responses in total (Table E3).

Association between PM_{2.5} and any symptom

Infants developed symptoms statistically significantly more often in accordance with PM_{2.5} levels (adjusted odds ratio [OR] per 10 µg/m³ increase of PM_{2.5}: 1.04, 95% confidence interval [CI]: 1.01-1.07, p=0.0028) (Table 2).

The effect of PM_{2.5} was observed mainly in spring and autumn. Analysis by

season showed similar patterns of OR elevations according to PM_{2.5} levels mainly in spring and autumn, when Asian dust sometimes flies over Japan, both in infants who had ever wheezed before the response and in those who had never wheezed (Figure 1).

Association between desert dust and any symptom

Infants developed symptoms statistically significantly more often in accordance with desert dust levels (OR per 0.1/km increase of desert dust: 1.17, 95% CI: 1.11–1.24, $p < 0.0001$) (Table E4). When including both PM_{2.5} and desert dust concentrations in a model, the effect of PM_{2.5} was diminished, but the effect of desert dust was not affected and remained significant (OR: 1.16, 95% CI: 1.09–1.23, $p < 0.0001$) (Table 2).

Sensitivity analyses with a model of the log score for outcome and a model where missing data regarding desert dust and PM_{2.5} were substituted by the average values of other regions on the day showed the robustness of the results. Further, to exclude possible information-bias, we analyzed data of mothers who did not get any PM_{2.5} or Asian dust information on the day of symptom development, which revealed that our effect estimation was robust (OR: 1.17, 95% CI: 1.11–1.24, $p < 0.0001$) (Table E5).

Sub-group analyses

Wheezers displayed two peaks in symptom development, whereas non-wheezers reported symptoms only at the time of exposure; in a lag analysis of the effects of desert dust on any symptom development in wheezers and

non-wheezers, the lag pattern differed between groups (Figure 2).

Analyses for each symptom revealed that wheezers reported nose symptoms on lag 4 and lag 5 days, followed by respiratory symptoms, both of which created a second peak in symptoms. Non-wheezers did not report a lag in respiratory symptoms (Figure E4, Figure E5). In addition, the risk increase in eye symptoms was observed in both wheezers and non-wheezers (data not shown).

Association between desert dust and secondary measures

The results of secondary outcomes were consistent with the primary outcome. Logistic regression analysis revealed that unplanned clinic visits, set as a secondary outcome, showed a lag pattern similar to that of symptom development (Figure E6). Day-care absence, another secondary outcome, was also significantly associated with desert dust level on lag 1 day and lag 2 day, but the second peak of the OR elevation was not clearly observed, possibly because we treated the first day of day-care absence as the outcome (Figure E7).

Possible countermeasures to symptom development

Receiving information on the particulate forecast, reducing time outdoors, closing windows, avoiding airing clothes and futons, and regular use of leukotriene receptor antagonists (LTRA) were significant effect modifiers. The OR for symptom development in wheezers whose mothers received forecast information on the day when the symptom questionnaire was sent out was lower than that for wheezers whose mothers did not receive forecast information

(Figure 3, Table E6a). Similarly, the OR was lower for subjects who had shorter outdoor durations, whose housing windows were closed, and whose clothes or futons were not aired on the day when the questionnaire was sent out (Figure 3, Table E6b, Table E6c, Table E6d, and Table E6e). The OR was also diminished for subjects who regularly used a LTRA (Figure 3, Table E6f). The OR reduction was unfortunately not clear for other drugs and for steroid inhalation, both of which had wide CIs (Figure 3, Table E6g, Table E6h). Notably, the numbers of subjects who regularly received other drugs or steroid inhalation were very small (n=31 and n=13, respectively; Table 1).

Discussion

This longitudinal study revealed that the risk of infants experiencing nose/eye/respiratory symptoms significantly increased as levels of PM_{2.5} rose. The increased risk was observed mainly in the spring and autumn months, when desert dust frequently flies over Japan. There was also an elevated risk for symptom development due to increased levels of desert dust. Secondary outcomes (unplanned clinic visits and absence from day-care) similarly showed elevated risks as the desert dust level rose. An increased risk was observed even among subjects who had never wheezed prior to the response, but the prolonged effect on symptoms was observed only among subjects who had reported wheezing prior to the response. Significant effect-modifiers included the mother's receipt of information about the PM forecast, the infant being outdoors on the day of symptom response, open windows anytime on the day of symptom response; and the regular use of LTRAs. As far as we know, this is the first report to show a clear association between desert dust and an increased risk of nose, eye, and respiratory symptom development in infants.

Asian dust has been associated with emergency department visits due to respiratory disease in preschool children at lag 0, lag day 1 and lag day 2 in one study,(28) and at lag day 2 and lag day 3 in another study.(29) Our findings that infants demonstrated 2 peaks in symptom development are consistent with the those results, and further revealed that the lag pattern of risk for symptom development was different between wheezers and non-wheezers: wheezers had 2 peaks in symptoms (lag day 1 and lag day 4), whereas non-wheezers developed symptoms only at the time of exposure. In the present study, the

wheezers were invited in October 2014 and non-wheezers in October 2015. Regarding differences in air pollution levels and variations from year to year, the overall time-course is shown in Figure E3. The levels of desert dust and PM_{2.5} measured during September 2014 – July 2016 and October 2015 – July 2016 were similar (data not shown). Furthermore, the correlation coefficients between the dust level on the day and the dust level on some previous days during September 2014 – July 2016 (wheezers) and October 2015 – July 2016 (non-wheezers) were similar (data not shown). Accordingly, we consider that the observed differences in reaction to desert dust on some lag days was not confounded by the difference in air pollution levels nor by periodic cycles of dust levels.

Particulates are thought to act as adjuvants in allergic responses.(46-48) Recent studies have demonstrated that particulates stimulate innate cells to release damage-associated molecular patterns (DAMPs), and that innate immune responses induced by DAMPs are required for the induction of adaptive immune responses.(47, 49) Recently, Kuroda *et al.* reported that particulates such as aluminum salts and silica induced death of alveolar macrophages, which then released interleukin-1 α as DAMPs. Furthermore, although adjuvants are generally thought to induce antigen-specific immune responses when administered concurrently with the antigen, Kuroda's study demonstrated that immune responses were activated even when antigen and adjuvants were administered separately to the lungs.(50) The delayed and sustained adjuvant effects of particulates on the lung in that study may explain our findings that the duration of effects of desert dust in wheezers was longer than that in

non-wheezers.

We also explored possible effective countermeasures against desert dust exposure in Japan. Findings from a previous study that examined the influence of outdoor PM levels on indoor PM levels during Asian dust events suggested that it was important to account for occupant behaviors, such as window-opening, when estimating residential exposure to PM.(39, 51) We found that symptom development was actually diminished in infants whose mothers received information about PM levels, whose outdoor durations were shorter, when windows were closed, and when clothes and futons were not aired outside. Furthermore, the risk was diminished in infants who took LTRAs regularly, which is consistent with previous findings in animal studies demonstrating that leukotrienes may play important roles in airway inflammation augmented by Asian dust. Kurai *et al.* reported that co-exposure to Asian dust and antigen caused both neutrophilic and eosinophilic airway inflammation, as demonstrated by increased numbers of neutrophils and eosinophils and levels of cysteinyl leukotrienes, dihydroxy-leukotrienes, and Th2 cytokines (interleukin-5 and interleukin-13) in bronchoalveolar lavage fluid (BALF).(52) Furthermore, both neutrophilic and eosinophilic airway inflammation were attenuated by the type 1 cysteinyl leukotriene receptor antagonist.(52) Although we encourage these countermeasures for those who experience symptoms upon exposure to desert dust, an RCT will be necessary to confirm the effectiveness of LTRA.

This study had the following limitations. Firstly, the study was observational and accordingly has constraints for causal inference. Secondly, infants' symptoms were reported by the mothers and not confirmed by physicians,

although this approach has become widely utilized.(53-55) Thirdly, we could not assess asthma severity or objective measure such as specific-IgE or skin prick test, and participants were classified as wheezers or non-wheezers according to the ISAAC questionnaire. Further studies will be required to examine whether desert dust exposure increases the risk of abnormality on objective measurements such as IgE level, lung function parameters, and skin prick test. Finally, LIDAR measurement was used for desert dust concentration, and PM components other than desert dust were not analyzed. If there were any pollutants that accompanied desert dust concentrations, we were not able to distinguish their potential affects.

The strengths of this study included its study design. Questionnaires were sent to mobile phones of the participants, who responded within a day. Thus, outcome data were collected while participants' memories were fresh, which we believe resulted in a very high response rate and contributed to the accuracy of data regarding symptoms, behavior, and regular use of asthma medications.

In conclusion, PM_{2.5} was associated with an increased risk of nose, eye, and respiratory symptoms that was mainly attributed to desert dust, not only in infants who had previously wheezed, but also in those who had never wheezed. For infants who experience such symptoms upon desert dust exposure, receipt of information by their mothers on the PM forecast, reducing their time outdoors, closing windows, avoiding airing clothes and futons, and regular use of LTRA will alleviate symptoms.

Acknowledgements

Kyoto Regional Centre: Ikuo Konishi, Toshio Heike, Takeo Nakayama, Yukuo Konishi, Tohshin Go, Keiko Sato, Miho Egawa, Yoshimitsu Takahashi, Motonobu Watanabe, Reiko Yasumi, Kyoko Hirabayashi, Masahito Morita, Kaori Konishi, Kumiko Kanatani, Research Coordinators, and members of the JECS Kyoto Management Committee

Toyama Regional Centre: Hidekuni Inadera, Kei Hamazaki, Yuichi Adachi, Akiko Tsuchida, and Research Coordinators

Tottori Regional Centre: Yasuaki Hirooka, Soji Fukumoto, Ryota Teshima, Takao Inoue, Youichi Kurozawa, Tasuku Harada, Susumu Kanzaki, Yoshihiro Maegaki, Kosaku Ohno, Tatsuya Koeda, Kazunari Onishi, Hiroki Amano, Toshio Masumoto, and Research Coordinators.

The authors would like to thank all participants of the study who contributed to a very high response rate; Prof. Toshiya Sato and Mr. Hisashi Noma for statistical support; Prof. Atsushi Shimizu and Prof. Nobuo Sugimoto for providing LIDAR data; Prof. Hiroshi Nitta, Prof. Hirohisa Takano, and Prof. Kayo Ueda for fruitful discussions; Toyama Prefectural Environmental Science Research Centre, Higashiosaka City Environmental Department Pollution Control Division, Kyoto Prefectural Government, Department of Culture and the Environment, Lake Biwa Environmental Research Institute, Kyoto City, Environmental Conservation Division of Toyama City Hall, and Tottori Prefectural Institute of Public Health and Environmental Science for providing air pollution data; Japan Weather Association for pollen data; Japan Meteorological Agency for meteorological data; and personnel at the hospitals and clinics that collaborated

on the JECS study.

Kumiko T Kanatani confirmed that written permission has been obtained from each person named in the Acknowledgements.

Kumiko T Kanatani had full access to all of the data in the study, and Yuichi Adachi takes responsibility for the integrity of the data and the accuracy of the data analyses.

Kumiko T Kanatani confirmed that written permission has been obtained from each person named in the Acknowledgements.

Kumiko T Kanatani had full access to all of the data in the study, and Yuichi Adachi takes responsibility for the integrity of the data and the accuracy of the data analyses.

Conflict of interest disclosures: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf.

Sources of support: This work was supported by the Environment Research and Technology Development Fund from the Ministry of the Environment of Japan [5-1555 (2015-2017)] and the Environmental Restoration and Conservation Agency, Japan (2014-2016), and conducted as an adjunct study to the Japan Environment and Children Study (JECS).

The findings and conclusions of this article are solely under the responsibility of the authors and do not represent the official views of the Japanese government.

This article is protected by copyright. All rights reserved

Figure legends

Figure 1 Odds ratio for any symptom development (symptom score >0) per 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ in each season.

Figure 2 Lag analysis for odds ratio for any symptom development (symptom score >0) per 0.1/km increase of desert dust in subjects who had ever/never wheezed before the response.

Figure 3 Odds ratio for any symptom development (symptom score >0) per 0.1/km increase of desert dust in each group defined by behavior on the day. See Table E6 for details.

Figure E1 The target locations of ‘Effects of desert dust exposure on children’s health’, an adjunct study of the Japan Environment and Children’s Study.

Figure E2 Participants in the Japan Environment and Children’s Study (JECS), adjunct study part 2, and the analysis population. Some non-wheezers at study entry experienced wheezing during the study, and their symptom responses after they experienced wheezing were analyzed as wheezers.

Figure E3 Time courses of daily $\text{PM}_{2.5}$ and desert dust levels in each location during the study period. Black: $\text{PM}_{2.5}$, Orange: desert dust

Figure E4 Lag analysis for odds ratio for nose symptom per 0.1/km increase in desert dust in those who had ever/never wheezed before the response.

- Model description •

$$\text{logit Pr}(Y = 1) = \beta_0 + \beta_1 X_1 + \dots + \beta_p X_p \quad (\text{single lag model})$$

Outcome (Y=1) : Nose symptom (Total of nose symptom score >0)

X₁: Desert dust

X_p: Age at answer, gender, area, number of siblings, housing style, temperature difference from the previous day, temperature difference within the day, average air pressure on the day, season

Figure E5 Lag analysis for odds ratio for respiratory symptom per 0.1/km increase in desert dust in those who had ever/never wheezed before the response

• Model description •

logit $\Pr(Y = 1) = \beta_0 + \beta_1 X_1 + \dots + \beta_p X_p$ (single lag model)

Outcome (Y=1) : Any respiratory symptom (Total of respiratory symptom score >0)

X₁: Desert dust

X_p: Age at answer, gender, area, number of siblings, average temperature on the day, temperature difference from the previous day, temperature difference within the day, average air pressure on the day, season

Figure E6 Lag analysis for odds ratio for unplanned clinic visits per 0.1/km increase in desert dust in those who had ever/never wheezed before the response

• Model description •

logit $\Pr(Y = 1) = \beta_0 + \beta_1 X_1 + \beta_2 X_2$ (single lag model)

Outcome (Y=1) : Unplanned clinic visits

X₁: Desert dust

X₂: Weekdays or Saturdays or Sundays and Holidays

Figure E7 Lag analysis for odds ratio for day-care absence per 0.1/km

increase in desert dust

- Model description •

logit $\Pr(Y = 1) = \beta_0 + \beta_1 X_1$ (single lag model)

Outcome (Y=1) : Day-care absence

X_1 : Desert dust

Table legends

Table 1 Characteristics of the subjects

Table 2 Adjusted odds ratio for any symptom development per 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ with (and without) desert dust in the model

Table E1 Distribution of air pollutants during the study period at each location

Table E2 Correlation coefficients among air pollutants at each location

Table E3 Distribution of symptom scores

Table E4 Adjusted odds ratio for any symptom development per 0.1/km increase of desert dust

Table E5 Adjusted odds ratio for any symptom development analyzed with data of those who did not get any $\text{PM}_{2.5}$ or desert dust information on the day

Table E6 Effect modification by each behavior

References

1. Matricardi PM. The allergy epidemic. In: Global atlas of allergy. Zurich: *European Academy of Allergy and Clinical Immunology* 2014:112-114.
2. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. *World Allergy Organ J* 2014;**7**(1):12.
3. Burbank AJ, Sood AK, Kesic MJ, Peden DB, Hernandez ML. Environmental determinants of allergy and asthma in early life. *J Allergy Clin Immunol* 2017;**140**(1):1-12.
4. Brunekreef B, Holgate ST. Air pollution and health. *Lancet* 2002;**360**(9341):1233-1242.
5. Kim KH, Jahan SA, Kabir E. A review on human health perspective of air pollution with respect to allergies and asthma. *Environ Int* 2013;**59**:41-52.
6. Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, et al. Association of improved air quality with lung development in children. *N Engl J Med* 2015;**372**(10):905-913.
7. Lu F, Xu D, Cheng Y, Dong S, Guo C, Jiang X, et al. Systematic review and meta-analysis of the adverse health effects of ambient PM_{2.5} and PM₁₀ pollution in the Chinese population. *Environ Res* 2015;**136**:196-204.
8. Rückerl R, Schneider A, Breitner S, Cyrus J, Peters A. Health effects of particulate air pollution: A review of epidemiological evidence. *Inhal Toxicol* 2011;**23**(10):555-592.
9. Dockery DW. Health effects of particulate air pollution. *Ann Epidemiol* 2009;**19**(4):257-263.
10. Strosnider HM, Chang HH, Darrow LA, Liu Y, Vaidyanathan A,

Strickland MJ. Age-specific associations of ozone and PM_{2.5} with respiratory emergency department visits in the US. *Am J Respir Crit Care Med* 2019;199(7):882-890.

11. Salimi F, Morgan G, Rolfe M, Samoli E, Cowie CT, Hanigan I, et al. Long-term exposure to low concentrations of air pollutants and hospitalisation for respiratory diseases: A prospective cohort study in Australia. *Environ. Int.* 2018;121:415-420.

12. U.S. Environmental Protection Agency. Integrated Science Assessment for Particulate Matter (Final Report). Washington, DC; 2009. EPA/600/R-08/139F. [cited; Available from: <http://epa.gov/ncea/isa/pm.htm> [Accessed 3 Jul 2018]

13. Boucher O, Randall D, Artaxo A, Bretherton C, Feingold G, Forster P, et al.. Clouds and Aerosols. In: Climate Change 2013: The Physical Science Basis. Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change [Stocker T.F., Qin D, Plattner D-K, et al. (eds.)]. Cambridge, UK and New York, NY: Cambridge University Press. 2013;571-657.

14. Mallone S, Stafoggia M, Faustini A, Gobbi GP, Marconi A, Forastiere F. Saharan dust and associations between particulate matter and daily mortality in Rome, Italy. *Environmen. Health Perspect.* 2011;119(10):1409-1414.

15. Middleton N, Yiallourous P, Kleanthous S, Kolokotroni O, Schwartz J, Dockery DW, et al. A 10-year time-series analysis of respiratory and cardiovascular morbidity in Nicosia, Cyprus: the effect of short-term changes in air pollution and dust storms. *Environ Health* 2008;7:39.

16. Perez L, Tobias A, Querol X, Künzli N, Pey J, Alastuey A, et al. Coarse particles from Saharan dust and daily mortality. *Epidemiology* 2008;**19**(6):800-807.
17. Prospero JM, Blades E, Naidu R, Mathison G, Thani H, Lavoie MC. Relationship between African dust carried in the Atlantic trade winds and surges in pediatric asthma attendances in the Caribbean. *Int J Biometeorol* 2008;**52**(8):823-832.
18. Karanasiou A, Moreno N, Moreno T, Viana M, de Leeuw F, Querol X. Health effects from Sahara dust episodes in Europe: literature review and research gaps. *Environ Int* 2012;**47**:107-114.
19. Chen YS, Sheen PC, Chen ER, Liu YK, Wu TN, Yang CY. Effects of Asian dust storm events on daily mortality in Taipei, Taiwan. *Environ Res* 2004;**95**(2):151-155.
20. Chan CC, Ng HC. A case-crossover analysis of Asian dust storms and mortality in the downwind areas using 14-year data in Taipei. *Sci Total Environ* 2011;**410-411**:47-52.
21. Kashima S, Yorifuji T, Tsuda T, Eboshida A. Asian dust and daily all-cause or cause-specific mortality in western Japan. *Occup Environ Med* 2012;**69**(12):908-915.
22. Kwon H-J, Cho S-H, Chun Y, Lagarde F, Pershagen G. Effects of the Asian dust events on daily mortality in Seoul, Korea. *Environmental Research* 2002;**90**(1):1-5.
23. Lee JT, Son JY, Cho YS. A comparison of mortality related to urban air particles between periods with Asian dust days and without Asian dust days in

Seoul, Korea, 2000-2004. *Environ Res* 2007;**105**(3):409-413.

24. Kojima S, Michikawa T, Ueda K, Sakamoto T, Matsui K, Kojima T, et al. Asian dust exposure triggers acute myocardial infarction. *Eur Heart J* 2017;**38**(43):3202-3208.

25. Cui LL, Zhang J, Zhang J, Zhou JW, Zhang Y, Li TT. Acute respiratory and cardiovascular health effects of an air pollution event, January 2013, Jinan, China. *Public Health* 2016;**131**:99-102.

26. Liu ST, Liao CY, Kuo CY, Kuo HW. The Effects of PM2.5 from Asian dust storms on emergency room visits for cardiovascular and respiratory diseases. *Int J Environ Res Public Health* 2017;**14**(4). pii: E428

27. Kanatani KT, Ito I, Al-Delaimy WK, Adachi Y, Mathews WC, Ramsdell JW, et al. Desert dust exposure is associated with increased risk of asthma hospitalization in children. *Am J Respir Crit Care Med* 2010;**182**(12):1475-1481.

28. Nakamura T, Hashizume M, Ueda K, Shimizu A, Takeuchi A, Kubo T, et al. Asian dust and pediatric emergency department visits due to bronchial asthma and respiratory diseases in Nagasaki, Japan. *J Epidemiol* 2016;**26**(11):593-601.

29. Yu HL, Chien LC, Yang CH. Asian dust storm elevates children's respiratory health risks: a spatiotemporal analysis of children's clinic visits across Taipei (Taiwan). *PLoS One* 2012;**7**(7):e41317.

30. Yu HL, Yang CH, Chien LC. Spatial vulnerability under extreme events: a case of Asian dust storm's effects on children's respiratory health. *Environ Int* 2013;**54**:35-44.

31. Watanabe M, Yamasaki A, Burioka N, Kurai J, Yoneda K, Yoshida A, et

- 671 al. Correlation between Asian dust storms and worsening asthma in Western
672 Japan. *Allergol Int* 2011;**60**(3):267-275.
- 673 32. Kanatani KT, Hamazaki K, Inadera H, Sugimoto N, Shimizu A, Noma H,
674 et al. Effect of desert dust exposure on allergic symptoms: A natural experiment
675 in Japan. *Ann Allergy Asthma Immunol* 2016;**116**(5):425-430.e427.
- 676 33. Chang CC, Lee IM, Tsai SS, Yang CY. Correlation of Asian dust storm
677 events with daily clinic visits for allergic rhinitis in Taipei, Taiwan. *J Toxicol
678 Environ Health A* 2006;**69**(3-4):229-235.
- 679 34. Chien LC, Lien YJ, Yang CH, Yu HL. Acute increase of children's
680 conjunctivitis clinic visits by Asian dust storms exposure - a spatiotemporal study
681 in Taipei, Taiwan. *PLoS One* 2014;**9**(10):e109175.
- 682 35. Ko R, Hayashi M, Hayashi H, Hayashi K, Kato H, Kurata Y, et al.
683 Correlation between acute conjunctivitis and Asian dust on ocular surfaces. *J
684 Toxicol Environ Health A* 2016;**79**(8):367-375.
- 685 36. Mulitza S, Heslop D, Pittauerova D, Fischer HW, Meyer I, Stuut JB, et al.
686 Increase in African dust flux at the onset of commercial agriculture in the Sahel
687 region. *Nature* 2010;**466**(7303):226-228.
- 688 37. Goudie AS. Dust storms: recent developments. *J Environ Manage*
689 2009;**90**(1):89-94.
- 690 38. Ozer P, Courel MF, Goudie AS. International year of deserts,
691 desertification and dust. *Africa Health*; 2006;**28**(4):1-3.
- 692 39. Kanatani KT, Adachi Y, Sugimoto N, Noma H, Onishi K, Hamazaki K, et
693 al. Birth cohort study on the effects of desert dust exposure on children's health:
694 protocol of an adjunct study of the Japan Environment & Children's Study. *BMJ*

Open 2014;**4**(6):e004863.

40. Nitta H. [Outline of the Japan Environment and Children's Study and the Framework of Genome Analysis]. *Nihon Eiseigaku Zasshi* 2016;**71**(1):91-93.

41. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health* 2014;**14**:25.

42. Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, et al. Baseline profile of participants in the Japan Environment and Children's Study (JECS). *J Epidemiol* 2018;**28**(2):99-104.

43. Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**(9537):733-743.

44. Häfner D, Reich K, Matricardi PM, Meyer H, Kettner J, Narkus A. Prospective validation of 'Allergy-Control-SCORE(TM)': a novel symptom-medication score for clinical trials. *Allergy* 2011;**66**(5):629-636.

45. Kanatani KT, Slingsby BT, Mukaida K, Kitano H, Adachi Y, Häfner D, et al. Translation and linguistic validation of the Allergy-CONTROL-ScoreTM for use in Japan. *Allergol Int* 2013;**62**(3):337-341.

46. Ichinose T, Yoshida S, Sadakane K, Takano H, Yanagisawa R, Inoue K, et al. Effects of asian sand dust, Arizona sand dust, amorphous silica and aluminum oxide on allergic inflammation in the murine lung. *Inhal Toxicol* 2008;**20**(7):685-694.

47. Kool M, Willart MA, van Nimwegen M, Bergen I, Pouliot P, Virchow JC,

et al. An unexpected role for uric acid as an inducer of T helper 2 cell immunity to inhaled antigens and inflammatory mediator of allergic asthma. *Immunity* 2011;**34**(4):527-540.

48. Kuroda E, Ishii KJ, Uematsu S, Ohata K, Coban C, Akira S, et al. Silica crystals and aluminum salts regulate the production of prostaglandin in macrophages via NALP3 inflammasome-independent mechanisms. *Immunity* 2011;**34**(4):514-526.

49. Marichal T, Ohata K, Bedoret D, Mesnil C, Sabatel C, Kobiyama K, et al. DNA released from dying host cells mediates aluminum adjuvant activity. *Nat Med* 2011;**17**(8):996-1002.

50. Kuroda E, Ozasa K, Temizoz B, Ohata K, Koo CX, Kanuma T, et al. Inhaled fine particles induce alveolar macrophage death and interleukin-1alpha release to promote inducible bronchus-associated lymphoid tissue formation. *Immunity* 2016;**45**(6):1299-1310.

51. Kanatani KT, Okumura M, Tohno S, Adachi Y, Sato K, Nakayama T. Indoor particle counts during Asian dust events under everyday conditions at an apartment in Japan. *Environ Health Prev Med* 2014;**19**(1):81-88.

52. Kurai J, Watanabe M, Sano H, Hantan D, Tohda Y, Shimizu E. Effects of Asian dust particles on the early-stage antigen-induced immune response of asthma in NC/Nga mice. *Int J Environ Res Public Health* 2016;**13**(11). pii: E1144.

53. Vissing NH, Jensen SM, Bisgaard H. Validity of information on atopic disease and other illness in young children reported by parents in a prospective birth cohort study. *BMC Med Res Methodol* 2012;**12**:160.

- 743 54. Cornish RP, Henderson J, Boyd AW, Granell R, Van Staa T, Macleod J.
744 Validating childhood asthma in an epidemiological study using linked electronic
745 patient records. *BMJ Open* 2014;**4**(4):e005345.
- 746 55. Arathimos R, Granell R, Henderson J, Relton CL, Tilling K. Sex
747 discordance in asthma and wheeze prevalence in two longitudinal cohorts. *PLoS*
748 *One* 2017;**12**(4):e0176293.
- 749

Table 1 Characteristics of the subjects

	Wheezers (n=515) *				Non-wheezers (n=973) *			
Age at entry, years [†]	2.2 ± 0.6 [‡]		0.4-4.6 [§]		2.6 ± 0.7 [‡]		0.9-4.1 [§]	
Weight at birth, grams [†]	3046 ± 388 [‡]		1628-4694 [§]		3044 ± 385 [‡]		1426-4282 [§]	
Gender	Female		Male		Female		Male	
	n	%	n	%	n	%	n	%
	228	44.4	286	55.6	535	55.0	437	45.0
Area	n		%		n		%	
Kyoto	157		30.5		307		31.6	
Toyama	214		41.6		427		43.9	
Tottori	144		28.0		239		24.6	
Full term birth [†]	No		Yes		No		Yes	
	11	5.2	202	94.8	10	2.4	413	97.6
Baby food at 6 months of age [†]	Not started		Started		Not started		Started	
	177	34.9	330	65.1	351	36.8	603	63.2
Mother's milk at 1 year of age [†]	Stopped		Continued		Stopped		Continued	
	120	24.3	374	75.7	264	27.9	684	72.2
Artificial milk at 1 year of age [†]	No		Yes		No		Yes	
	311	62.7	185	37.3	594	62.5	357	37.5
Distance from the main trunk road								
~30 m	163		32.7		305		32.2	

30~50 m	107	21.4	186	19.6
50 m~	229	45.9	456	48.2
blank	16	3.1	26	2.7
Smoking around the infant [†]				
Rarely	381	77.3%	768	81.2%
Occasionally	99	20.1%	153	16.2%
Often	13	2.6%	25	2.6%
blank	22	4.3%	27	2.8%
Mother's history of asthma	No		Yes	
	430	83.5	85	16.5
Mother's history of allergic rhinitis	No		Yes	
	285	55.3	230	44.7
Mother's history of atopic dermatitis	No		Yes	
	404	78.5	111	21.6
Father's history of asthma	No		Yes	
	431	84.8	77	15.2
Father's history of allergic rhinitis	No		Yes	
	296	58.3	212	41.7
Father's history of atopic dermatitis	No		Yes	
	437	86.0	71	14.0
Asthma diagnosis at entry	No		Yes	
	390	78.5	107	21.5
Regular use of medicine				

Leukotriene blockers	Yes		No			
	56	12.9	379	87.1		
Other allergy drugs	Yes		No			
	31	7.1	404	92.9		
Steroid inhalation	Yes		No			
	13	3.0	422	97.0		

* Wheezers and non-wheezers: Wheezers were infants who had wheezed before study entry, non-wheezers were infants who had not wheezed before study entry, [†] Refers to Japan Environment and Children's Study (tentative data),

[‡] mean $\pm$ SD, [§] minimum - max

Table 2 Adjusted odds ratio for any symptom development per 10 $\mu\text{g}/\text{m}^3$ increase of $\text{PM}_{2.5}$ with (and without) desert dust in the model

	Odds ratio	95% confidence interval		p value
$\text{PM}_{2.5}$ ($10\mu\text{g}/\text{m}^3$)	1.01 (1.04)	0.98 (1.01)	1.04 (1.07)	0.506 (0.0028)
Asian dust (per 0.1/km)	1.16	1.09	1.23	<.0001
Wheeze experience before the response	1.44 (1.41)	1.27 (1.23)	1.64 (1.61)	<.0001 (<.0001)
Number of siblings	0.90 (0.90)	0.84 (0.84)	0.97 (0.97)	0.0082 (0.0058)
Average temperature on the day ($^{\circ}\text{C}$)	0.99 (0.99)	0.99 (0.99)	1.00 (1.00)	0.0459 (0.0010)
Temperature difference from the previous day ($^{\circ}\text{C}$)	0.99	0.98	1.00	0.0205
Temperature difference within the day ($^{\circ}\text{C}$)	1.01 (1.01)	1.01 (1.01)	1.02 (1.02)	<.0001 (<.0001)
Average air pressure (hPa)	1.00	1.00	1.01	0.0827
Toyama *	0.73 (0.72)	0.63 (0.63)	0.84 (0.83)	<.0001 (<.0001)
Tottori *	0.91 (0.89)	0.77 (0.76)	1.07 (1.04)	0.2618 (0.1450)

Winter [†]	0.88 (0.86)	0.80 (0.80)	0.96 (0.94)	0.0049 (0.0003)
Spring [†]	0.85 (0.89)	0.79 (0.83)	0.93 (0.96)	0.0001 (0.0031)
Summer [†]	0.56 (0.57)	0.51 (0.52)	0.62 (0.63)	<.0001 (<.0001)
Female [‡]	0.78 (0.76)	0.69 (0.68)	0.87 (0.85)	<.0001 (<.0001)
Age at the response (year)	0.73 (0.73)	0.67 (0.68)	0.79 (0.79)	<.0001 (<.0001)

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Backward elimination method with cut-off p value of 0.1 was conducted.

Complete dataset analysis (61,976 answers for 1,321 infants).

“Temperature difference from the previous day” and “Average air pressure” did not remain in the model without desert dust as the consequence of the backward elimination.

* Compared with subjects in Kyoto

[†] Compared with autumn

[‡] Compared with male

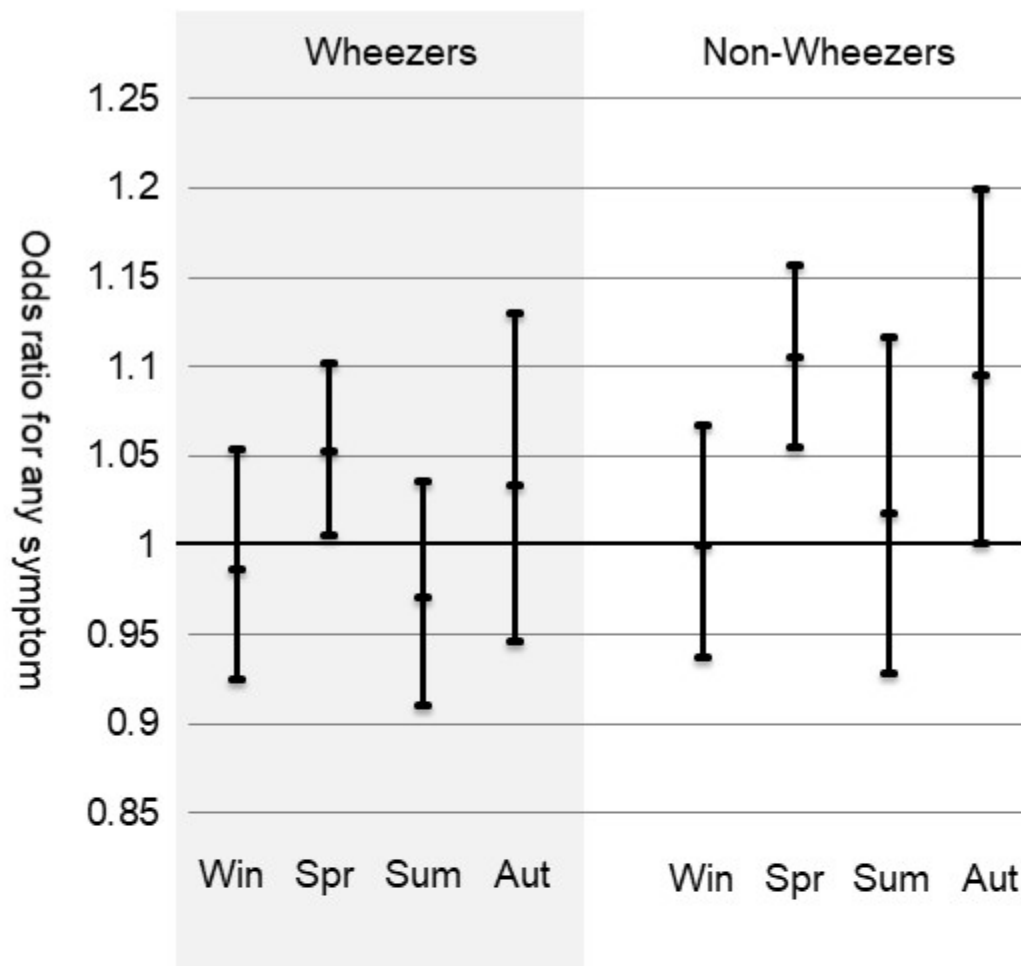


Figure 1 Odds ratio for any symptom development (symptom score >0) per 10 µg/m³ increase of PM_{2.5} in each season.

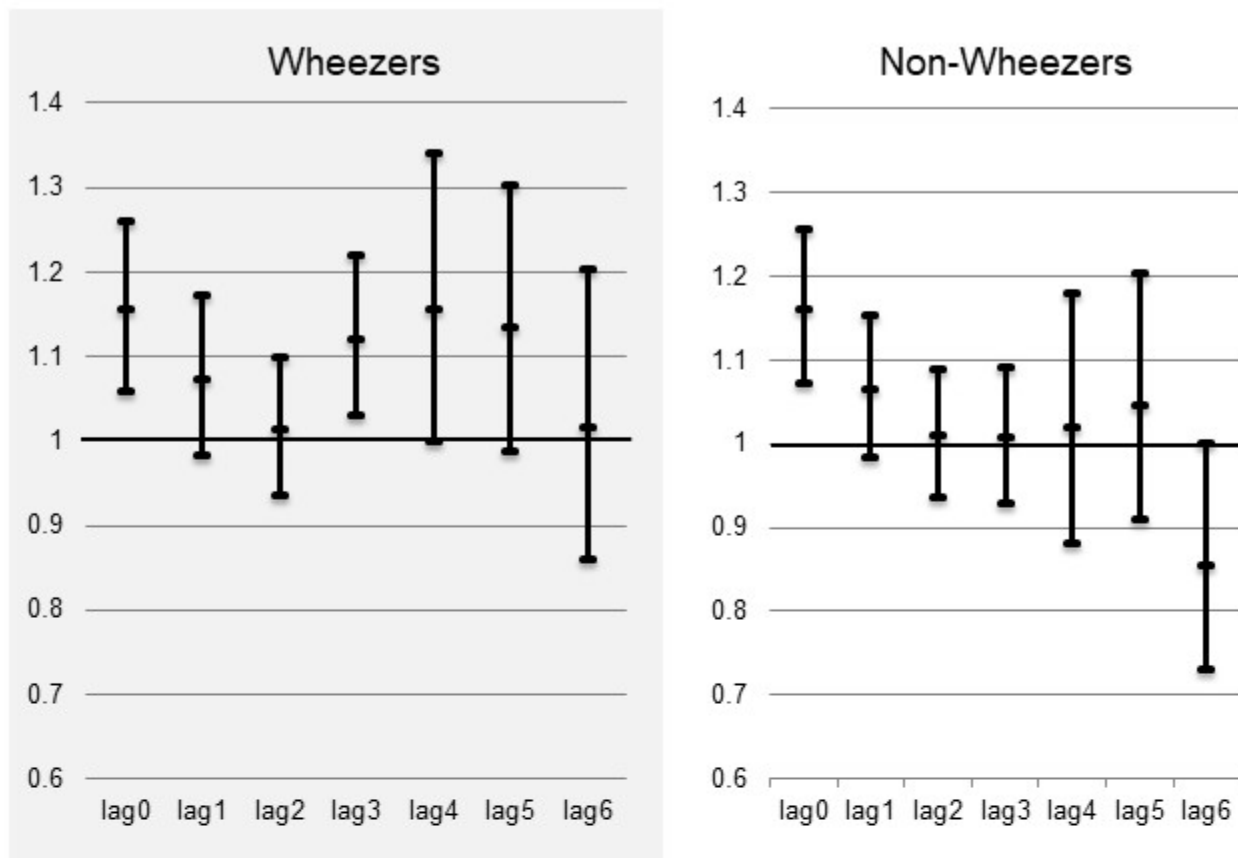


Figure 2 Lag analysis for odds ratio for any symptom development (symptom score >0) per 0.1/km increase of desert dust in subjects who had ever/never wheezed before the response.

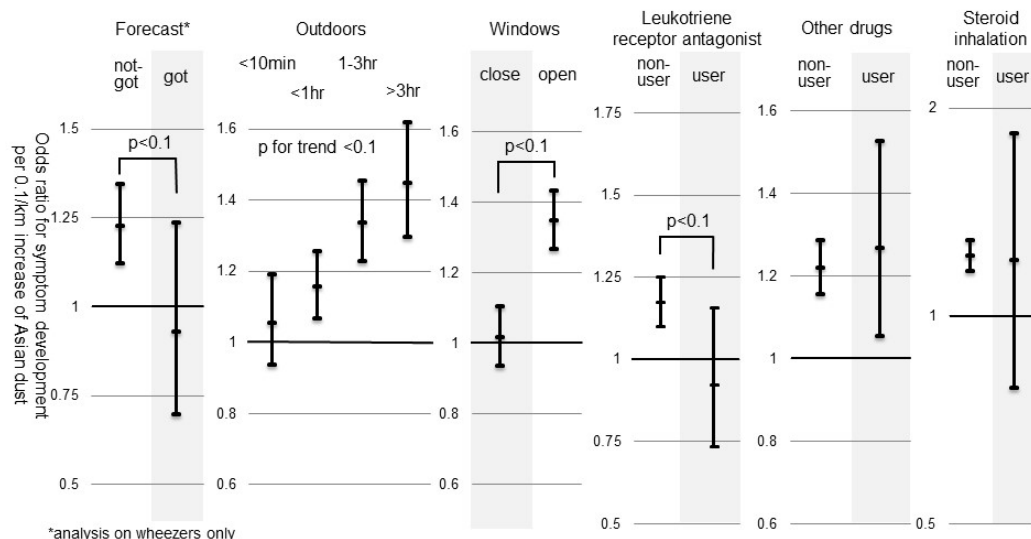


Figure 3 Odds ratio for any symptom development (symptom score > 0) per 0.1/km increase of desert dust in each group defined by behavior on the day. See Table E6 for details.

all_14166_f3.jpg



Figure E1 The target locations of ‘Effects of desert dust exposure on children’s health’, an adjunct study of the Japan Environment and Children’s Study.

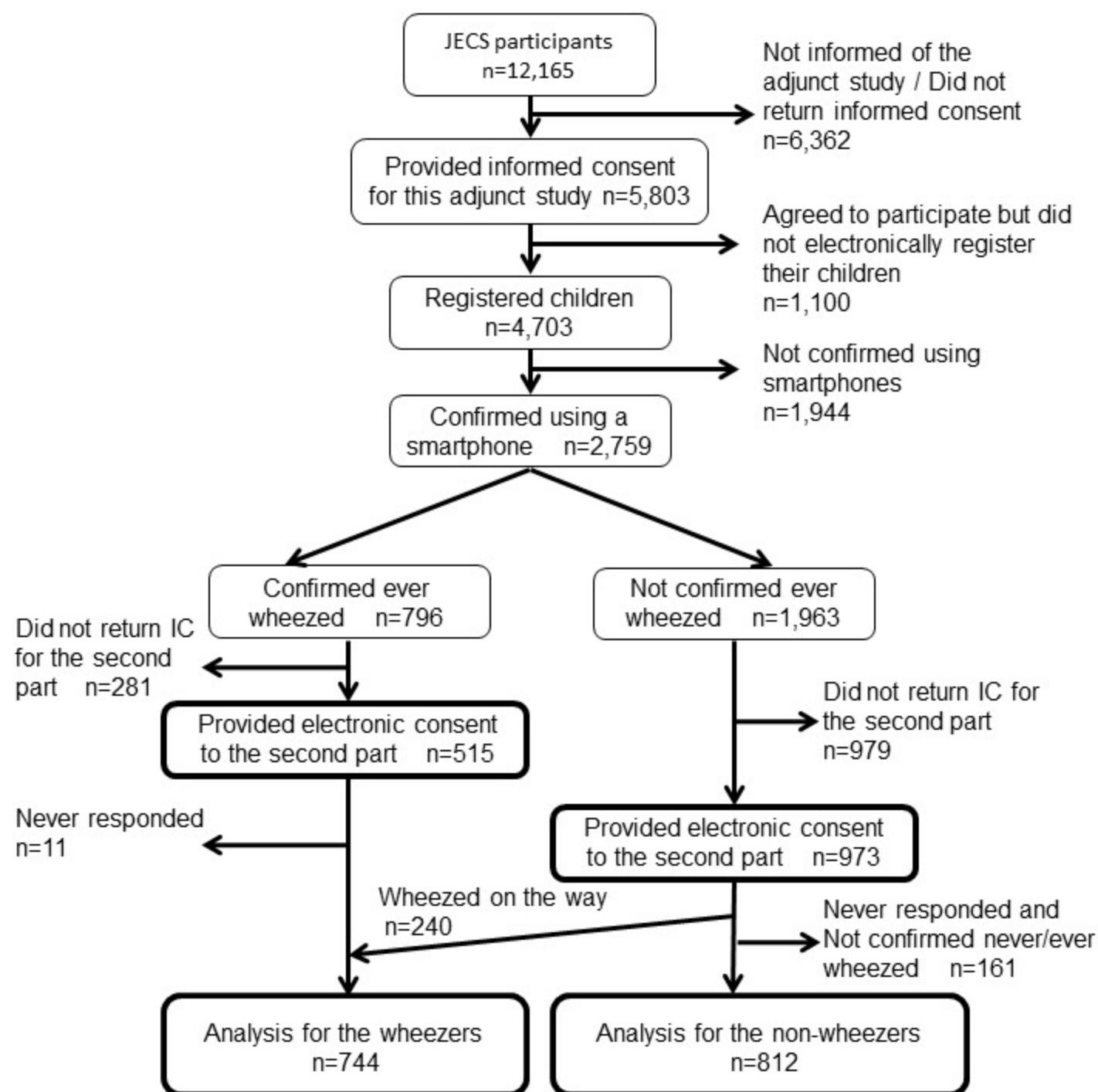


Figure E2 Participants in the Japan Environment and Children's Study (JECS), adjunct study part 2, and the analysis population.

Some non-wheezers at study entry experienced wheezing during the study, and their symptom responses after they experienced wheezing were analyzed as wheezers.

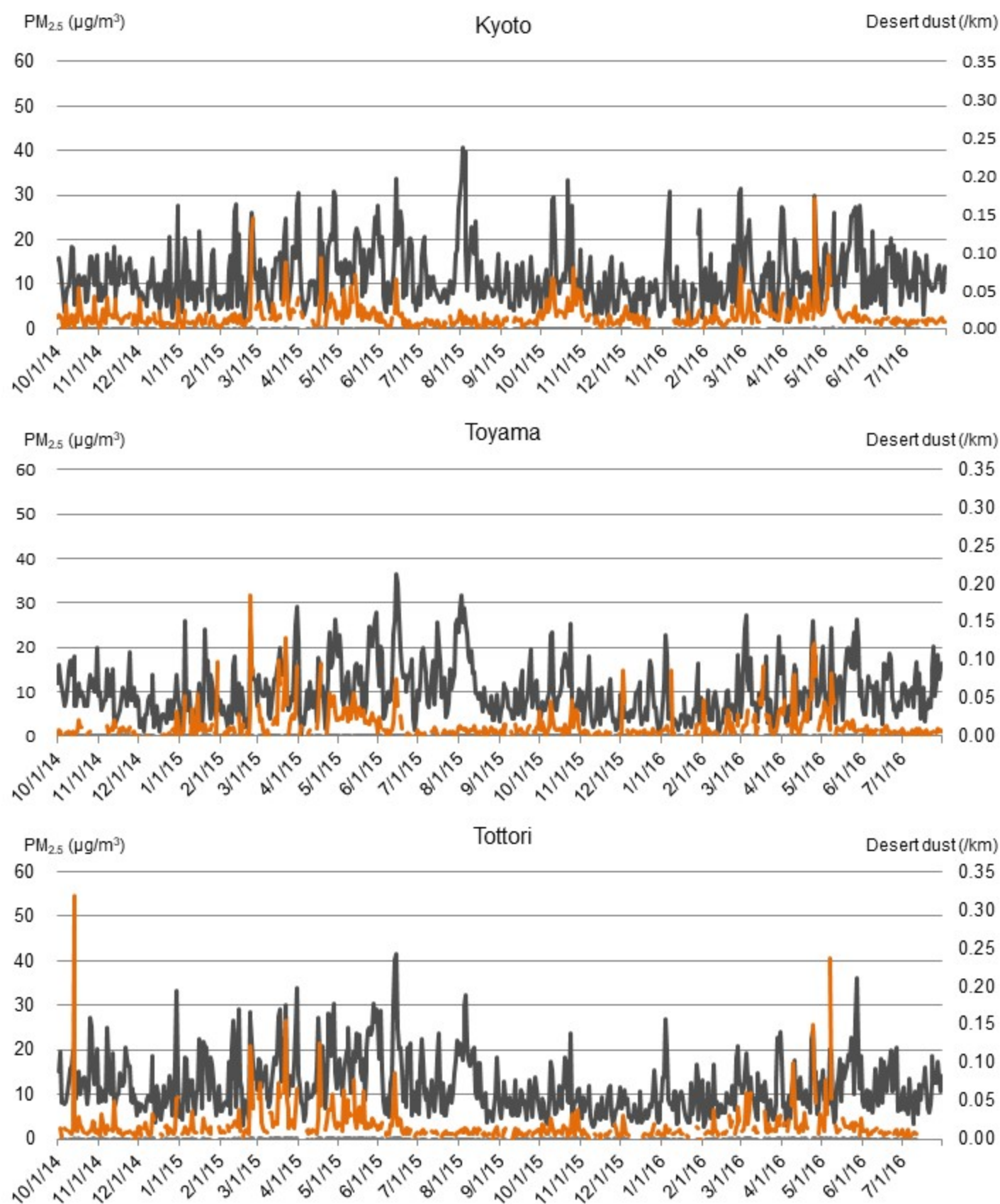


Figure E3 Time courses of daily $PM_{2.5}$ and desert dust levels in each location during the study period. Black: $PM_{2.5}$, Orange: desert dust

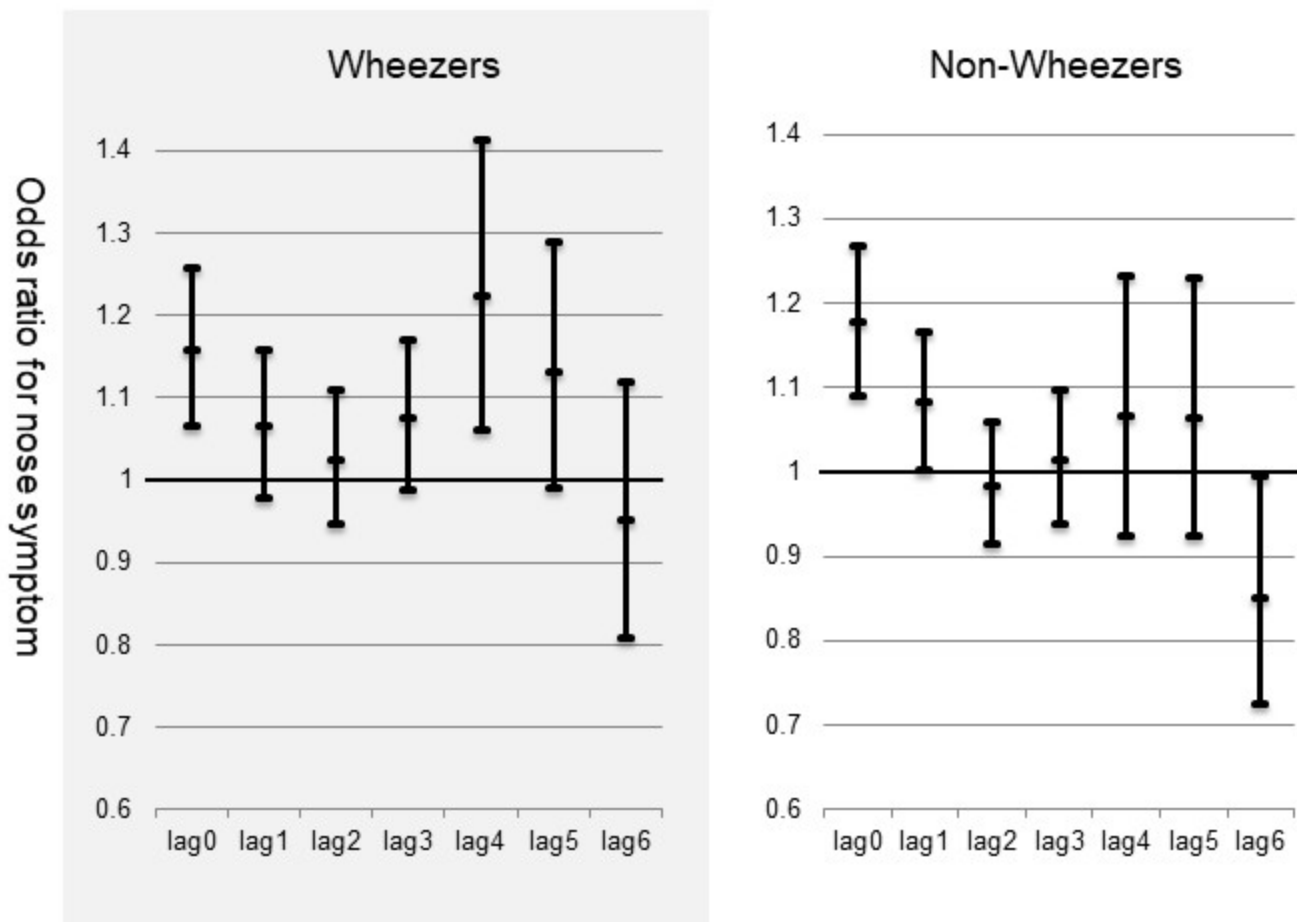


Figure E4 Lag analysis for odds ratio for nose symptom per 0.1/km increase in desert dust in those who had ever/never wheezed before the response.

● **Model description** ●

$\text{logit Pr}(Y = 1) = \beta_0 + \beta_1 X_1 + \dots + \beta_p X_p$ (single lag model)

Outcome (Y=1) : Nose symptom (Total of nose symptom score >0)

X_1 : Desert dust

X_p : Age at answer, gender, area, number of siblings, housing style, temperature difference from the previous day, temperature difference within the day, average air pressure on the day, season

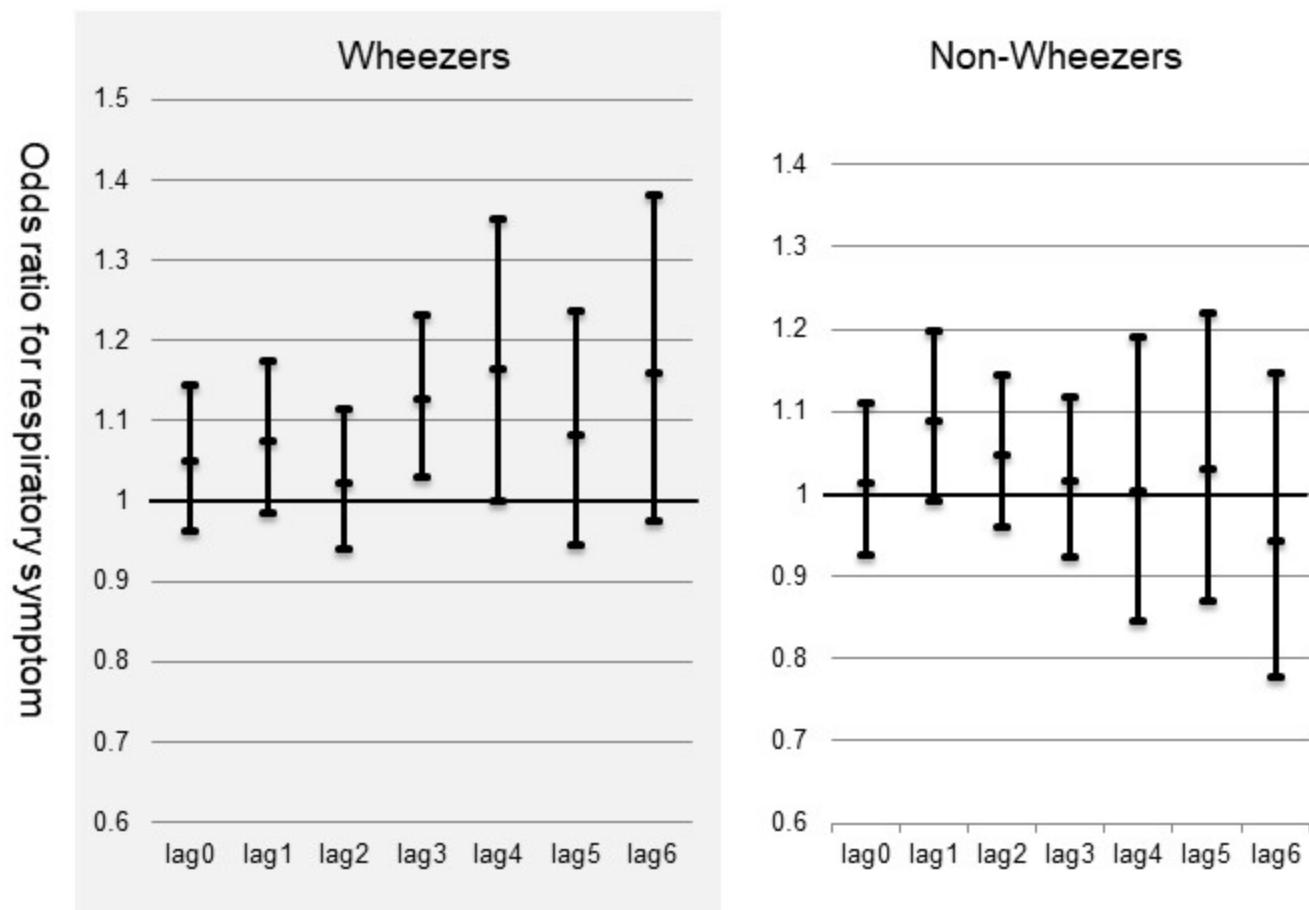


Figure E5 Lag analysis for odds ratio for respiratory symptom per 0.1/km increase in desert dust in those who had ever/never wheezed before the response

● **Model description** ●

$\text{logit Pr}(Y = 1) = \beta_0 + \beta_1 X_1 + \dots + \beta_p X_p$ (single lag model)

Outcome (Y=1) : Any respiratory symptom (Total of respiratory symptom score >0)

X_1 : Desert dust

X_p : Age at answer, gender, area, number of siblings, average temperature on the day, temperature difference from the previous day, temperature difference within the day, average air pressure on the day, season

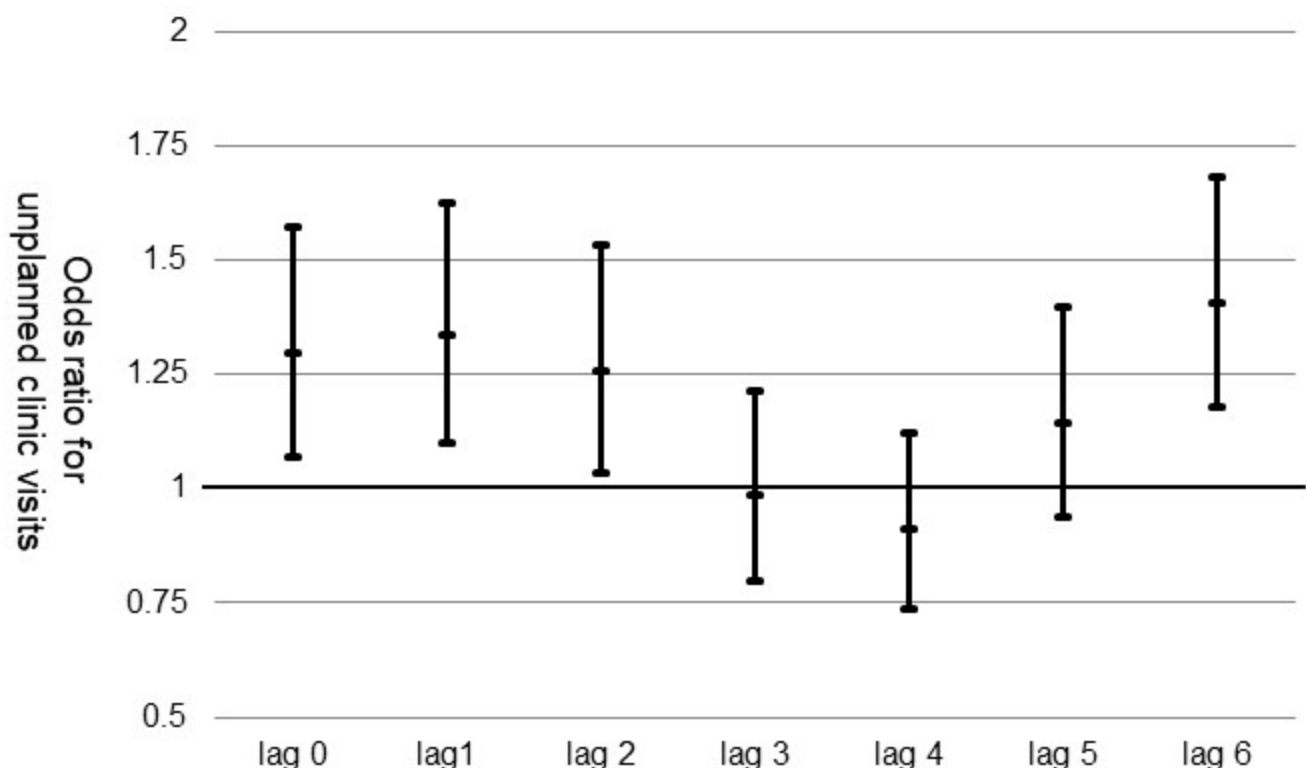


Figure E6 Lag analysis for odds ratio for unplanned clinic visits per 0.1/km increase in desert dust in those who had ever/never wheezed before the response

● Model description ●

$\text{logit Pr}(Y = 1) = \beta_0 + \beta_1 X_1 + \beta_2 X_2$ (single lag model)

Outcome (Y=1): Unplanned clinic visits

X_1 : Desert dust

X_2 : Weekdays or Saturdays or Sundays and Holidays

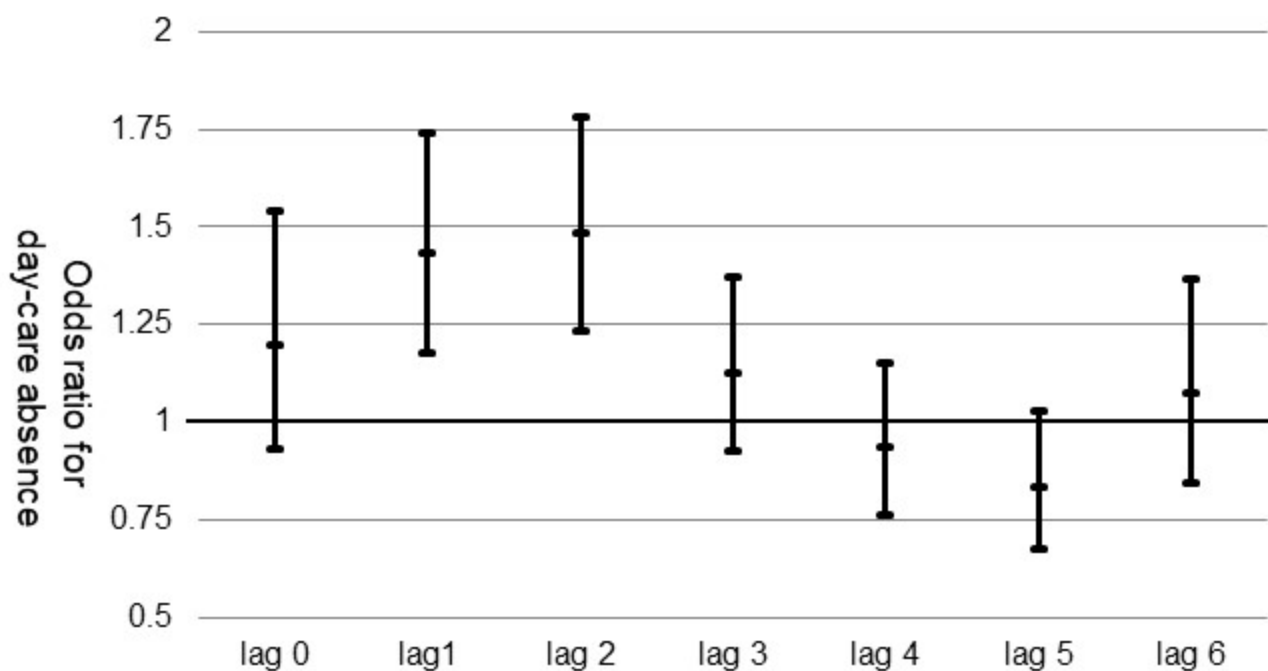


Figure E7 Lag analysis for odds ratio for day-care absence per 0.1/km increase in desert dust

● Model description ●

$\text{logit Pr}(Y = 1) = \beta_0 + \beta_1 X_1$ (single lag model)

Outcome ($Y=1$): Day-care absence

X_1 : Desert dust

1 Table E1 Distribution of air pollutants during the study period at each location

	Location	Mean	SD	25 %tile	50 %tile	75 %tile	n (days)
SO ₂ (ppb)	Kyoto	3.3	0.9	3	3	4	641
	Toyama	0.93	0.56	1	1	1	549
	Tottori	0.69	0.85	0	1	1	641
NO ₂ (ppb)	Kyoto	11.5	4.9	8	11	14	634
	Toyama	8.3	4.2	5	7	10	548
	Tottori	5.6	2.7	4	5	7	606
Ox* (ppb)	Kyoto	36.7	14.6	27	35	45	635
	Toyama	39.1	12.3	31	38	45	549
	Tottori	39.3	13.1	31	38	47	633
PM _{2.5} (µg/m ³)	Kyoto	11.9	6.6	7.2	10.6	15.1	637
	Toyama	10.1	6.2	5.5	9.0	13.4	640
	Tottori	11.8	6.4	7.2	10.2	15.2	641
Dust† (/km)	Kyoto	0.017	0.017	0.008	0.012	0.020	549
	Toyama	0.016	0.021	0.004	0.008	0.018	500
	Tottori	0.017	0.021	0.007	0.011	0.018	505
Sphere particles (/km)	Kyoto	0.120	0.069	0.068	0.110	0.157	545
	Toyama	0.117	0.062	0.072	0.106	0.151	489
	Tottori	0.066	0.048	0.036	0.056	0.084	497

2 * Ox was assessed based on 8-hour average.

3 † Dust was assessed based on 12-hour average (06:00-18:00) at 135 m height
4 from the ground.

5 Other pollutants were assessed based on 24-hour average.

6 NO₂, nitrogen dioxide; Ox, photochemical oxidants; PM, particulate matter; SD,
7 standard deviation; SO₂, sulfur dioxide;

8

9 Table E2 Correlation coefficients among air pollutants at each location

		SO ₂	NO ₂	Ox	PM _{2.5}	Dust
NO ₂	Kyoto	0.25	1			
	Toyama	0.29	1			
	Tottori	0.39	1			
Ox	Kyoto	0.46	-0.43	1		
	Toyama	0.22	-0.40	1		
	Tottori	0.06	-0.14	1		
PM _{2.5}	Kyoto	0.73	0.32	0.39	1	
	Toyama	0.31	0.08	0.42	1	
	Tottori	0.31	0.13	0.47	1	
Dust	Kyoto	0.39	0.12	0.37	0.46	1
	Toyama	0.30	0.05	0.46	0.40	1
	Tottori	0.33	0.20	0.50	0.57	1
Sphere particles	Kyoto	0.32	0.31	0.01	0.51	0.20
	Toyama	0.30	0.18	0.31	0.58	0.18
	Tottori	-0.02	0.09	0.22	0.58	0.13

10 Spearman's rank correlation was used.

11 NO₂, nitrogen dioxide; Ox, photochemical oxidants; PM, particulate matter; SO₂:

12 sulfur dioxide

13

14 Table E3 Distribution of symptom scores

	Score	Number of responses with symptom development /number of responses	Mean of score	SD	Min	25th Percentile	50th Percentile	75th Percentile	90th Percentile	Max
Wheezers at entry ^a	total	17,257 /26,778	2.60	3.44	0	0	1	4	7	30
	– nose	15,539 /26,778	1.72	2.16	0	0	1	3	5	12
	– eyes	4,049 /26,778	0.28	0.85	0	0	0	0	1	9
	– resp.	8,480 /26,778	0.61	1.23	0	0	0	1	2	9
Non-wheezers at entry ^a	total	23,103 /42,223	1.71	2.48	0	0	1	2	5	25
	– nose	20,644 /42,223	1.21	1.74	0	0	0	2	4	12
	– eyes	3,705 /42,223	0.13	0.53	0	0	0	0	0	9
	– resp.	9,965 /42,223	0.36	0.82	0	0	0	0	1	9

15 ^a Wheezers at entry and non-wheezers at entry: Wheezers at entry were infants who had ever wheezed before study
16 entry, and non-wheezers at entry were those who had not wheezed.
17 SD, standard deviation

Table E4 Adjusted odds ratio for any symptom development per 0.1/km increase of desert dust

	Odds ratio	95% confidence interval		p value
Asian dust (per 0.1/km)	1.17	1.11	1.24	<.0001
Average temperature on the day (°C)	0.99	0.99	1.00	0.0232
Temperature difference within the day (°C)	1.01	1.00	1.02	0.0012
Toyama *	0.73	0.63	0.84	<.0001
Tottori *	0.91	0.78	1.08	0.2789
Winter †	0.87	0.80	0.95	0.0017
Spring †	0.86	0.79	0.93	0.0002
Summer †	0.56	0.51	0.62	<.0001
Female ‡	0.78	0.69	0.87	<.0001
Age at the response (year)	0.73	0.67	0.79	<.0001
Number of siblings	0.90	0.84	0.98	0.0090
Wheeze experience before the response	1.44	1.27	1.64	<.0001

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix was used.

Backward elimination method with cut-off p value of 0.1 was conducted.

Complete dataset analysis (43,044 answers for 1,234 infants).

* Compared with the subjects in Kyoto

† Compared with autumn

‡ Compared with male

Table E5 Adjusted odds ratio for any symptom development, analyzed for data on those who did not get any PM_{2.5} or desert dust information on the day

	Odds ratio	95% confidence interval		p value
Asian dust (per 0.1/km)	1.17	1.10	1.25	<.0001
Average temperature on the day (°C)	0.99	0.99	1.00	0.0857
Temperature difference within the day (°C)	1.02	1.01	1.03	<.0001
Toyama *	0.71	0.61	0.82	<.0001
Tottori *	0.91	0.76	1.08	0.2721
Winter †	0.91	0.82	1.00	0.0566
Spring †	0.85	0.77	0.93	0.0007
Summer †	0.55	0.49	0.63	<.0001
Female ‡	0.78	0.69	0.89	0.0001
Age at the response (years)	0.76	0.69	0.85	<.0001
Number of siblings	0.90	0.83	0.98	0.0107
Wheeze experience before the response	1.44	1.27	1.65	<.0001

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix was used.

* Compared with the subjects in Kyoto

† Compared with autumn

‡ Compared with male

Table E6 Effect modification by each behavior

Table E6a Effect modification of symptom development by receipt of particulate information

	Odds ratio	95% confidence interval		p value
Received information	1.54	1.23	1.91	<.0001
Asian dust (per 0.1/km) when particulate information was not received	1.23	1.12	1.34	<.0001
Interaction term	0.76	0.56	1.02	0.0648

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Analysis of the data for those who had ever wheezed before the response.

Table E6b Effect modification of symptom development by outdoor duration

	Odds ratio	95% confidence interval		p value
Outdoor duration (per 1 category increase)	0.90	0.87	0.92	<.0001
Asian dust when outdoor duration was "less than 10 minutes" (per 0.1/km increase)	1.04	0.95	1.14	0.36
Interaction term	1.12	1.07	1.18	<.0001

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Outdoor duration was treated as ordered category; 0: less than 10 minutes, 1: 10 minutes - 1 hour, 2: 1-3 hours, 3: more than 3 hours.

Table E6c Effect modification of symptom development by closing windows

	Odds ratio	95% confidence interval		p value

Closing windows	1.22	1.15	1.29	<.0001
Asian dust when windows were open (per 0.1/km)	1.35	1.27	1.43	<.0001
Interaction term	0.76	0.68	0.83	<.0001

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Table E6d Effect modification of symptom development by avoiding clothesline

	Odds ratio	95% confidence interval		p value
Avoid clothesline	1.14	1.08	1.21	<.0001
Asian dust when clothesline was used (per 0.1/km)	1.40	1.29	1.53	<.0001
Interaction term	0.81	0.73	0.89	<.0001

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Table E6e Effect modification of symptom development by avoiding airing futons

	Odds ratio	95% confidence interval		p value
Avoid airing futons	1.07	1.00	1.15	0.0596
Asian dust when futons were aired (per 0.1/km)	1.38	1.22	1.58	<.0001
Interaction term	0.89	0.76	0.99	0.040

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Table E6f Effect modification of symptom development by regular use of LTRA

	Odds ratio	95% confidence interval		p value
Regular use of LTRA	2.26	1.93	2.64	<.0001
Asian dust when LTRA was not regularly used (per 0.1/km)	1.24	1.17	1.31	<.0001

Interaction term	0.79	0.64	0.96	0.0183
------------------	------	------	------	--------

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

LTRA: leukotriene receptor antagonist

Table E6g Effect modification of symptom development by regular use of medications other than LTRA

	Odds ratio	95% confidence interval		p value
Regular use of medications other than LTRA	1.42	1.16	1.73	0.0006
Asian dust when medication other than LTRA was not used (per 0.1/km)	1.22	1.15	1.29	<.0001
Interaction term	1.04	0.85	1.26	0.6902

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.

Adjusted by sex and age at the response.

LTRA: leukotriene receptor antagonist

Table E6h Effect modification of symptom development by regular use of steroid inhalation

	Odds ratio	95% confidence interval		p value
Regular inhalation of steroid	1.49	1.00	2.25	0.0561
Asian dust when steroid was not regularly inhaled (per 0.1/km)	1.22	1.16	1.29	<.0001
Interaction term	0.98	0.64	1.51	0.9336

Generalized estimating equations logistic regression analysis with exchangeable correlation matrix.