



Effect of Asian dust on respiratory symptoms among children with and without asthma, and their sensitivity

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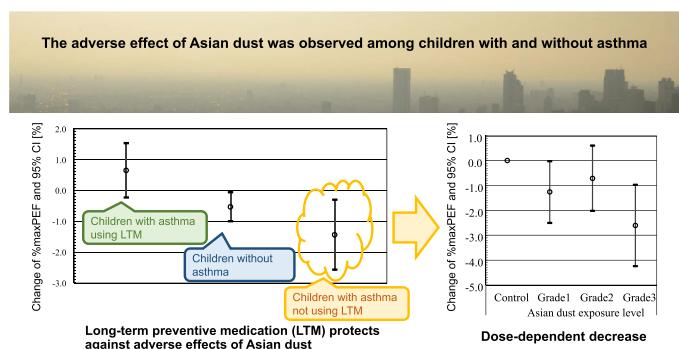
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HIGHLIGHTS

- The adverse effect of Asian dust was observed among children with and without asthma.
- Children with asthma not using medication were more susceptible to Asian dust.
- Long-term preventive medication protects against adverse effects of Asian dust.

GRAPHICAL ABSTRACT



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ABSTRACT

There has been little study on the effect of Asian dust exposure on respiratory symptoms among children who are vulnerable to environmental factors. In this panel study, we investigated the effect of Asian dust on respiratory symptoms among children with and without asthma, and their sensitivity.

Children attending two elementary schools (137 total), and 23 children with asthma from cooperating medical institutions in Fukuoka prefecture were recruited. Subjects measured peak expiratory flow rate (PEF), and recorded asthma-like symptoms, cough, nasal symptoms and use of medication in a diary from April 1, 2013 to June 30, 2013. To assess exposure to Asian dust, we used Light Detection and Ranging (LIDAR) data. For the analysis of the association between Asian dust and respiratory symptoms, the case-crossover design and generalized estimating equation (GEE) models were used. Taking individual sensitivity to respiratory aggravation into consideration, the subjects were classified into three groups: children without asthma, children with asthma who

Abbreviations: CA, children with asthma not using long-term preventive medication; CA-LTM, children with asthma using long-term preventive medication; GEE, generalized estimating equation; NO₂, Nitrogen dioxide; Ox, photochemical oxidant; PEF, Peak expiratory flow rate; PM_{2.5}, Particulate matter less than 2.5 μm in aerodynamic diameter; SPM, Suspended particulate matter; %maxPEF, the ratio of measured peak expiratory flow rate against the maximum peak expiratory flow rate of the subject.

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do not use long-term preventive medication (CA) and children with asthma who use long-term preventive medication (CA-LTM).

For CA, Asian dust exposure was significantly associated with asthma-like symptoms, with a hazard ratio of 5.17 (95%CI: 1.02–26.12) at Lag0, and the change in %maxPEF, -1.65% (95%CI: $-2.82, -0.48$) at Lag0. For children without asthma, a statistically significant association was found between Asian dust exposure and the change in %maxPEF, -0.56% (95%CI: $-1.31, -0.08$) at Lag1. However, no adverse effects were observed in CA-LTM. Temperature had significant effects on %maxPEF for three groups. Asian dust, photochemical oxidant and pollen caused simultaneously additive adverse effects on nasal symptoms for children without asthma.

This study suggests the possibility that long-term preventive medication to manage asthma may suppress aggravation of respiratory symptoms due to Asian dust and may be an effective prevention.

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1. Introduction

Asian dust is a phenomenon (Hashizume et al., 2010; Hasunuma et al., 2019) of soil particles originating in the dry areas of the Mongolia and China being picked up by strong winds, taken to an altitude of several thousand meters, then carried by westerly winds until it settles to the surface in areas of east Asia including Japan. In west Asia, dust storms also have been occurring originating from in the neighboring deserts (Gheybi et al., 2014). Recently, the association between exposure to Asian dust and mortality (Chan and Ng, 2011; Kashima et al., 2016; Kashima et al., 2012; Lee et al., 2014; Lee et al., 2013), hospitalization (Geravandi et al., 2017; Kanatani et al., 2010; Kang et al., 2012; Ueda et al., 2010; Wang et al., 2014) and medical institution visits from respiratory disorders (Khaefi et al., 2017; Nakamura et al., 2016; Park et al., 2016; Yu et al., 2012) have been reported. In these studies, statistical data are used, but changes in the symptoms of individuals targeted are not followed. To plan policies to prevent adverse health effects due to Asian dust, it is important to clarify which populations have high sensitivity to Asian dust and the degree to which health is affected.

Up until now, panel studies following symptoms and pulmonary function indicators such as peak expiratory flow rate (PEF) over a designated period have primarily focused on adult subjects (Higashi et al., 2014a; Higashi et al., 2014b; Onishi et al., 2012; Onishi et al., 2015; Otani et al., 2014; Otani et al., 2011; Watanabe et al., 2012; Watanabe et al., 2015a). In a study following adult asthma patients over four years, it was observed that symptoms in adult asthma patients are significantly influenced by factors related to individual sensitivity (Watanabe et al., 2012). A case control study conducted among adult subjects in Iran showed that exposure to dust storm increased allergic inflammation (Gheybi et al., 2014).

On the other hand, there are only three panel studies targeting children, who are considered to have a higher sensitivity than adults. Hong et al., studied elementary school students in Seoul and reported a significant association between Asian dust and decreases in PEF (Hong et al., 2010). Watanabe et al. studied elementary school students in Matsue City, Japan and reported that there was a significant decrease in PEF after exposure to Asian dust in 2012, but no significant decrease in 2013 (Watanabe et al., 2015b). Nakamura et al. recruited 110 children with asthma in Nagasaki prefecture, Japan and reported that a consistent association between Asian dust and decrease in PEF, however, Asian dust was not associated with the number of asthma attacks (Nakamura et al., 2020). These findings suggest that there also be individual sensitivity among children. In addition, since one study has reported that it is difficult to detect the effect of air pollution in pediatric asthma patients because of management with long-term medication (Hasunuma et al., 2018), it is necessary to take the use of long-term medication into consideration.

Therefore, this study aims to investigate the association between Asian dust exposure and respiratory symptoms among children with and without asthma, and their sensitivity.

2. Methods

2.1. Subjects

A panel study was conducted for children ages 6–12 years in Fukuoka prefecture, Japan. 137 children attending two elementary schools, and 23 children with asthma regularly visiting cooperating medical institutions were recruited into the study (160 children in total). After receiving informed consent from their parents, information including birth date, gender, and past history of allergic diseases was obtained using a medical questionnaire.

Of the 137 children attending two elementary schools, 22 who answered “yes” to the question, “Do you have bronchial asthma?” or were receiving treatment for asthma were regarded as “children with asthma”. Thus, the number of healthy children and children with asthma were 115 and 45, respectively.

2.2. Outcome assessment

Study participants were asked to record in a diary any asthma-like symptoms, cough and nasal symptoms and use of medication during the study period from April 1, 2013 to June 30, 2013. From the diary record, “asthma-like symptoms” were defined as selecting any of the following: chest pain (severe attack), chest pain on exercise (moderate attack) or cough during exercise (minor attack). “Nasal symptoms” were defined as selecting any of the following: runny nose, stuffy nose or sneezing.

Use of medication was classified into three groups: (1) medication for attacks, (2) medication for respiratory tract infection, and (3) long-term medication for asthma control. The use of (1) medication for attacks or (2) medication for respiratory tract infection itself was considered as an outcome. Since use of (3) long-term medication for attacks controls daily symptoms and has been reported to suppress the effect of air pollution on respiratory symptoms, it was used as a criterion to exclude children using long-term medication.

In addition, the objective indicator for respiratory function, PEF, was measured twice a day (morning and evening) during the study period and PEF was recorded in the diary. A Clement Clarke Mini-Wright peak flow meter was used for PEF measurements. The method for using the peak flow meter was explained to the study participants in advance and practice was conducted.

2.3. Exposure assessment

To assess exposure to Asian dust, we used Light Detection and Ranging (LIDAR) data measured at Kyushu University in Fukuoka City. This LIDAR data has been available since April 5, 2013. LIDAR measurements utilize the fact that optical characteristics of particles are dependent on their shape, and this is used to distinguish Asian dust from other particles (Shimizu et al., 2004). While air pollutant particles derived from exhaust gas are spherical, Asian dust particles are not. LIDAR uses polarized waves of light to distinguish this difference in shape and it is

possible to distinguish and observe Asian dust and spherical substances such as air pollutants other than Asian dust which cannot be distinguished by the naked eye. In LIDAR measurements, the laser beam is attenuated by scattering and absorption by aerosol particles, etc. The Asian dust extinction coefficient of the non-spherical particle component is estimated using the backscattering coefficient from LIDAR and polarization measurements. If the Asian dust extinction coefficient is over 0.1 /km, it can be determined that Asian dust is present (Kaneyasu et al., 2012).

In this study, to further increase the precision of determining specific daily exposure to Asian dust, it was defined as days that satisfy the following criteria from other preceding studies (Hasunuma et al., 2019; Nakamura et al., 2015; Nakamura et al., 2016):

1. The daily maximum suspended particulate matter (SPM) concentration was over 50 $\mu\text{g}/\text{m}^3$.
2. The daily maximum Asian dust extinction coefficient as measured by LIDAR was more than 0.05/km.
3. The correlation coefficient between the hourly Asian dust extinction coefficient and hourly SPM concentration was significant ($p < 0.01$).

2.4. Meteorological data, pollen and other air pollutants

Meteorological data (temperature, humidity, atmospheric pressure) were used from the Fukuoka District Meteorological Observatory.

Pollen data were obtained from the Fukuoka monitoring station in the pollen observation system operated by the Ministry of the Environment, Government of Japan (Ministry of the Environment Government of Japan, 2020). This pollen data are measured with an automatic cedar pollen counter and the unit is mean pollen count per hour (count/ m^3). Pollen data were available from April 1, 2013 to June 2, 2013.

Hourly air pollutant concentration data, including photochemical oxidant (Ox), nitrogen dioxide (NO_2), particulate matter less than 2.5 μm in aerodynamic diameter ($\text{PM}_{2.5}$), and SPM were obtained from air pollution monitoring stations, and were provided by the Ministry of the Environment Government of Japan. The air pollutant data used for analysis was the mean of concentrations provided by monitoring stations in the municipalities of the elementary schools and cooperating medical institutions.

2.5. Statistical analysis

We used the Welch's t-tests to compare air pollutants and climate factors on Asian dust days and non-Asian dust days.

For the analysis of the association between Asian dust and respiratory symptoms, the case-crossover design was used. For the analysis of the association between Asian dust and PEF, the generalized estimating equation (GEE) model was used. Taking individual sensitivity of children with or without asthma into consideration, the subjects were classified into three groups: children without asthma, children with asthma who do not use long-term preventive medication (CA) and children with asthma who use long-term preventive medication (CA-LTM).

Regarding the case-crossover design, in the same way as in a matched case-control analysis, case-crossover design assigned the days of symptom occurrence as the case day, and comparisons were made with control days chosen on the same day of the week earlier or later in the same month. The advantage of this design is that it controls for time trends, seasonality, and potential confounding caused by individual characteristics such as gender, race and age (Maclure, 1991; Maclure and Mittleman, 2000; Nitta et al., 2010). The hazard ratio of Asian dust exposure was estimated using logistic regression analysis with respiratory symptoms as the outcome variable and Asian dust exposure as the explanatory variable. Respiratory symptoms include asthma-like symptoms, cough, nasal symptoms, use of medication for attacks and use of medication for respiratory tract infection. Considering the possibility of a lag before health effects from Asian dust exposure

occur, the effect on the day of Asian dust exposure (Lag 0), one day later (Lag 1), and two days later (Lag 2) were investigated. Adjustment variables included in the analysis model were temperature drop (maximum temperature on the previous day minus minimum temperature on the day) and atmospheric pressure (mean of the day) because they had been reported to be significantly related to the respiratory symptoms (Hasunuma et al., 2019; Ueda et al., 2010). Also, pollen levels were added as a covariate for the analysis of nasal symptoms. National holidays were excluded from the analysis since the trend of air pollutant concentration on these holidays differs from those on ordinary days. Analysis was performed using the PHREG procedure in SAS release 9.2.

The GEE model was used to estimate the change in the ratio of measured PEF against the maximum PEF of the subject (hereinafter abbreviated as “%maxPEF”) upon Asian dust exposure. To ensure statistical power, the PEF readings for morning and evening were pooled in the main analysis. We also examined the morning-evening variation in the sub-analysis. Adjustment variables included in the analysis model were age, gender, passive smoke, air temperature and humidity. Lag0, Lag1 and Lag2 were used for exposure to Asian dust. Regarding air temperature, the value at 8:00 was used for morning and 22:00 was used for evening. Regarding humidity, the mean relative humidity for the day was used. Self-measurement of PEF by children has been suggested to be unreliable until they become experienced. The value for days 1, 2 and 3 when starting measurement was significantly lower statistically than the mean for days 20 to 22 (paired t-test, $p > 0.05$). Therefore, data from day 4 of PEF measurement were used for data analysis. The GENMOD procedure of SAS release 9.2 (U.S. SAS Institute) was used for GEE analysis.

Since a statistically significant decrease in %maxPEF from the time of Asian dust arrival was observed, an investigation into whether there is a dose-response relationship between Asian dust exposure level and decrease in %maxPEF was conducted. We defined the Asian dust exposure level as the cumulative of Asian dust extinction coefficient between 0 and 2 days following an event and classified into Grade1 to Grade3 (Grade1: <5 /km, Grade2: ≥ 5 to < 10 /km, Grade3: ≥ 10 /km). Then we estimated the change in %maxPEF upon Asian dust exposure level at Grades 1, 2 and 3 compared to Asian dust exposure level zero (Control).

Air pollution exists as a complex mixture. Air pollutants may be influenced by the toxicity of the mixture of air pollutants (WHO Regional Office for Europe, 2013). In our previous studies investigating the association between respiratory symptoms and Ox, we observed a statistically significant association among children with and without asthma between Ox concentration and %maxPEF, cough and nasal symptoms. To evaluate the effect of mixture of Asian dust and Ox, we conducted an analysis adding Ox as a covariate.

This study was performed with the ethical approval of the Fukuoka National Hospital Ethical Committee of the National Hospital Organization.

3. Result

3.1. Subject characteristics

Characteristics of the study participants are in Table 1. The number of children without asthma, CA and CA-LTM were 115, 21 and 24, respectively. Regarding the frequency of all respiratory symptoms, it was the highest in CA-LTM. These symptoms comprised the use of medication for attacks, use of medication for respiratory tract infection, asthma-like symptoms, cough, and nasal symptoms.

We identified 15 days on which Asian dust arrived during the survey period (Table 2). Not only particulate matter concentrations ($\text{PM}_{2.5}$ and SPM), but also gaseous air pollutants concentrations (Ox and NO_2) on Asian dust days were statistically higher than on control days. Also, temperature drop and humidity differed significantly between Asian dust days and non-Asian dust days.

Table 1
Subject characteristics.

Group	Children without asthma		CA		CA-LTM	
Number, n	115		21		24	
	Gender					
Male, n (%)	53	(46.1)	8	(38.1)	18	(75.0)
Female, n (%)	62	(53.9)	13	(61.9)	6	(25.0)
Age in years, mean (SD)	8.9	(1.4)	9.2	(1.6)	8.5	(1.8)
Passive Smoke, %	31.3		14.3		20.8	
Frequency of respiratory symptoms ^a						
Use of medications for attacks, %	0.1		1.4		3.2	
Use of medications for respiratory tract infection, %	0.9		3.5		11.9	
Asthma-like symptoms, %	1.3		1.3		3.7	
Coughing, %	6.1		7.8		15.8	
Nasal symptoms, %	14.6		15.5		34.0	
%maxPEF, mean (SD)	85.0	(10.7)	83.8	(11.1)	87.6	(9.1)

Abbreviations: CA, Children with asthma not using long-term preventive medications; CA-LTM, Children with asthma using long-term preventive medications; %maxPEF, the ratio of measured peak expiratory flow rate against the maximum peak expiratory flow rate of the subject; SD: Standard deviation.

^a Total number of days with each symptom / Total number of observation days (%).

3.2. Association between Asian dust and respiratory symptoms

The cross-over analysis results of the relationship between Asian dust and respiratory symptoms are presented in Fig. 1. Regarding the relationship with asthma-like symptoms, a statistically significant relationship was found with Lag0 in CA and hazard ratio for Asian dust exposure was 5.17 (95%CI: 1.02, 26.12). No statistically significant relationship was found in for children without asthma and CA-LTM. Regarding the relationship with cough, the hazard ratio for Asian dust exposure (Lag0) was not statistically significant in CA and healthy children, but exceeded 1 (1.18 (95%CI: 0.70, 1.98), 1.26 (95%CI: 0.98, 1.62, $p = 0.07$), respectively). No statistically significant relationship was found for CA-LTM. Regarding nasal symptoms, a statistically significant relationship was found for Lag0 in CA and children without asthma, and the hazard ratio for Asian dust exposure was 1.76 (95%CI: 1.15, 2.69), 1.31 (95%CI: 1.09, 1.57), respectively. No significant relationship was found for CA-LTM.

Regarding relationship with “Use of medication for attacks” and “Use of medication for respiratory tract infection”, there was no statistically significant relationship showing that there is a higher risk with the arrival of Asian dust for any of the three groups.

3.3. Association between Asian dust and %maxPEF

The analysis results of the association between Asian dust and change of %maxPEF at Lag0 to Lag2 days using the GEE model, adjusted for age, gender, passive smoke, temperature and humidity are shown in Fig. 2. For children without asthma, the change of %maxPEF followed a significantly decreasing trend for Lag1 and Lag2 upon Asian dust arrival and the change for Lag 1 and Lag2 were -0.56% (95%CI: $-1.03, -0.08$), -0.54% (95%CI: $-1.01, -0.07$), respectively. For CA, the change in %maxPEF showed a statistically significantly decreasing trend for Lag0, and Lag2 and the change for Lag0 and Lag2 were -1.65% (95%CI: $-2.82, -0.48$), -1.44% (95%CI: $-2.58, -0.31$), respectively. No significant decrease was found for CA-LTM. We further examined the morning-evening variation in the sub-analysis. The results showed that the decreases of %maxPEF were observed in the morning (see Fig. S1).

Since a statistically significant decrease in %maxPEF from the time of Asian dust arrival was observed, we investigated whether there is a dose-response relationship between Asian dust exposure level and decrease in %maxPEF. We defined the Asian dust exposure level as the accumulation of Asian dust extinction between 0 and 2 days following an event and classified into Grade1 to Grade3. Then we estimated the change in %maxPEF upon Asian dust exposure level at Grades 1, 2 and 3 compared to Asian dust exposure level zero (Control). Fig. 3 shows the change of %maxPEF by Asian dust exposure level compared to Asian dust exposure level zero (control), using the GEE model adjusted for age, gender, passive smoke, temperature and humidity. The greatest decrease in %maxPEF was observed with the highest level of Asian dust (Grade 3) among CA with a change of -2.61% (95%CI: $-4.25, -0.97$). The dose-dependent decrease in %maxPEF was not so clearly found for children without asthma.

3.4. Other air pollutants and climate factors

We present the hazard ratio for respiratory symptoms and the change of %maxPEF further adjusted for Ox as other air pollutants in Fig. S2 and S3. These adjustments did not change the results substantially, although the significant effects of Asian dust were attenuated. It is noteworthy that relating to nasal symptoms for children without asthma, the hazard ratio of Asian dust, Ox per 10 ppb and pollen at Lag0 were 1.20 (95%CI: 0.99, 1.46), 1.07 (95%CI: 0.98, 1.16) and 1.10 (95%CI: 1.04, 1.17), respectively. These results indicated that those pollutants cause simultaneously additive adverse effects on nasal symptoms.

In regard to climate factors, we show the effect of climate factors on respiratory symptoms and %maxPEF in Table S1 and S2. Temperature

Table 2
Air pollutants and climatic factors on Asian dust days and control days during study period in Fukuoka city.

	Asian dust days (n = 15)					Non-Asian dust days (n = 72)					t-test
	Mean	SD	25th	50th	75th	Mean	SD	25th	50th	75th	p-value
Air pollutants											
Asian dust extinction coefficient, km^{-1}	0.067	0.034	0.03	0.07	0.10	0.024	0.023	0.01	0.02	0.03	<0.001
Pollen, counts/ m^3	9.5	9.1	5.2	6.8	11.3	16.1	15.5	6.0	12.2	20.5	0.055
O _x , ppb	51.9	11.7	48.0	55.2	59.9	41.2	11.5	34.8	41.9	49.0	0.004
NO ₂ , ppb	16.7	5.5	12.5	18.5	21.2	12.2	4.3	9.5	11.8	14.8	0.008
PM _{2.5} , $\mu\text{g}/\text{m}^3$	37.8	14.4	27.2	37.5	51.4	18.9	9.1	13.2	18.1	23.1	<0.001
SPM, $\mu\text{g}/\text{m}^3$	43.1	15.0	30.6	42.4	55.1	22.7	10.1	16.1	21.5	28.1	<0.001
Climatic factors											
Temperature, °C	20.9	2.0	19.1	21.4	22.1	19.6	4.9	15.9	21.0	23.5	0.119
Temperature drop ^a , °C	9.1	1.7	7.4	9.1	10.6	7.5	2.6	5.6	7.4	9.0	0.007
Humidity, %	60.5	9.9	55.0	59.0	68.0	69.5	14.0	59.0	69.0	81.0	0.007
Atmospheric pressure, hPa	1009.9	3.6	1007.4	1008.8	1011.7	1009.2	5.6	1004.5	1009.5	1013.8	0.541

Abbreviations: SD, standard deviation; O_x, photochemical oxidant; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter 2.5 μm or less in diameter; SPM, suspended particulate matter.

^a Maximum temperature on the previous day minus minimum temperature on the day.

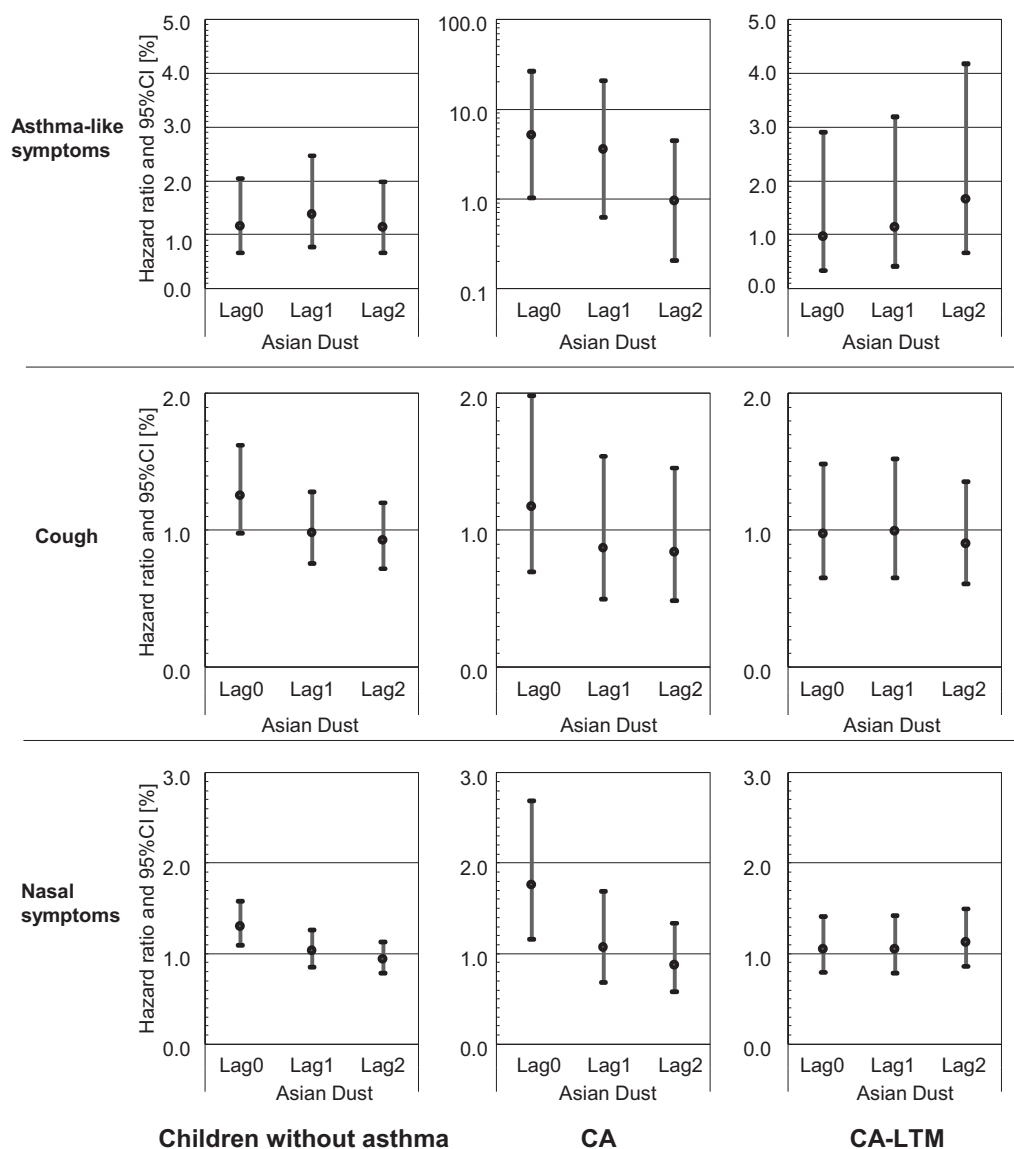


Fig. 1. Association between Asian dust and respiratory symptoms at Lag0 - Lag2 days using case-crossover design, adjusted for temperature drop and atmospheric pressure. Pollen amount was added as a covariate for the analysis of nasal symptoms. Abbreviations: CA, Children with asthma not using long-term preventive medications; CA-LTM, Children with asthma using long-term preventive medications.

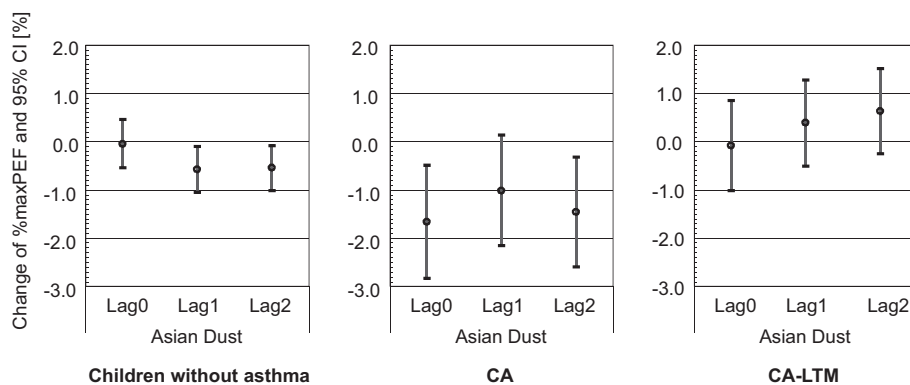


Fig. 2. Association between Asian Dust and change of %maxPEF at Lag0 - Lag2 days using GEE model, adjusted for age, gender, passive smoke, temperature and humidity. Abbreviations: CA, Children with asthma not using long-term preventive medications; CA-LTM, Children with asthma using long-term preventive medications; %maxPEF, the ratio of measured peak expiratory flow rate against the maximum peak expiratory flow rate of the subject.

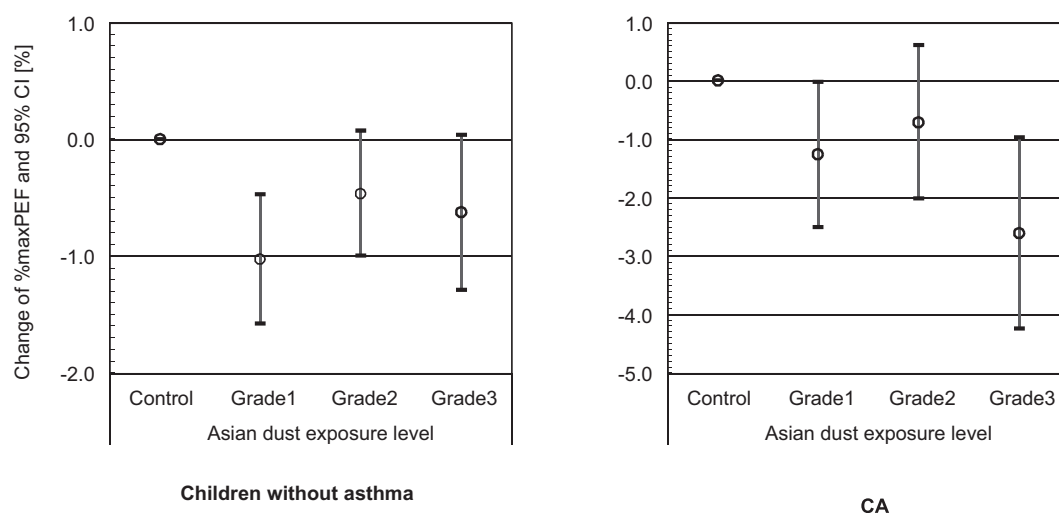


Fig. 3. Change of %maxPEF by Asian dust exposure level compared to Asian dust exposure level zero (control), using GEE model adjusted for age, gender, passive smoke, temperature and humidity. The Asian dust exposure level was defined as the cumulative of Asian dust extinction coefficient between 0 and 2 days following an event and classified into Grade1 to Grade3. (Grade1: <5 /km, Grade2: ≥ 5 to <10 /km, Grade3: ≥ 10 /km). Abbreviations: CA, Children with asthma not using long-term preventive medications; %maxPEF, the ratio of measured peak expiratory flow rate against the maximum peak expiratory flow rate of the subject.

has found to have significant effects on %maxPEF for three groups. Humidity has also a significant impact on %maxPEF for CA and children without asthma. Atmospheric pressure has a significant effect on cough among CA.

4. Discussion

This study investigated the relationship between Asian dust, respiratory symptoms and %maxPEF in children with and without asthma, taking the use of medication into consideration. The results showed that for children with asthma, Asian dust exposure was significantly associated with asthma-like symptoms, nasal symptoms and a decrease in % maxPEF. The hazard ratio for asthma-like symptoms was 5.17 (95%CI: 1.02, 26.12) at Lag0. For children without asthma, a statistically significant association was found with nasal symptoms and a decrease in % maxPEF. No significant association was found with cough, but a hazard ratio of 1.26 (95%CI: 0.98, 1.62) was estimated. For CA-LTM, no adverse effects were observed.

In addition to recording the significant extent to which Asian dust aggravates respiratory symptoms in children, this study defines decreasing levels of sensitivity across three groups of children, from CA to children without asthma and finally CA-LTM. This result is consistent with the findings of our previous study that investigated the degree to which respiratory symptoms were aggravated by ambient air pollution (Hasunuma et al., 2018). Li et al. conducted a review of panel studies and reported that positive associations between air pollutants and pulmonary symptoms were found more often in children with asthma than in healthy subjects. In addition, children with asthma have high respiratory tract sensitivity and it has been reported that symptoms are aggravated as the atmospheric environment worsens (Li et al., 2012). The results of this study support the findings that CA are a population with extremely high sensitivity to Asian dust. From 2010, for prevention and early intervention, the Japanese Pediatric Guideline for the Treatment and Management of Asthma recommended the use of long-term medication for management. In this study, there was no significant association between Asian dust arrival and %maxPEF and respiratory symptoms in CA-LTM. This suggests that the use of long-term medication is effective in preventing the aggravation of respiratory symptoms due to Asian dust exposure for children with asthma. Previous studies on Asian dust and respiratory symptoms were population-based and most studies evaluated association with death, hospitalization or clinic visits. For example, Kanatani et al. investigated the association with

hospitalization for aggravation of pediatric asthma and reported that the odds ratio of hospitalization on a severe Asian dust day was 1.71 (95%CI: 1.18, 2.48) (Kanatani et al., 2010). Nakamura et al. investigated the association with visits to the Nagasaki City Night-time Emergency Center and reported that the odds ratio of emergency outpatient visits by school children for bronchial asthma was 1.84 (95%CI: 1.21, 2.79) (Nakamura et al., 2016). Geravandi et al. reported the number of hospital admissions during dust storm is significantly higher than during normal days in Ahvaz, Iran (Geravandi et al., 2017). In this study, in stratified analysis restricted to children with asthma not using long-term preventive medication, the hazard ratio (Lag0) for asthma-like symptoms was 5.17 (95%CI: 1.02, 26.12) and showed a higher risk than for previous population-based studies, but as mentioned earlier, this analysis was restricted to a population with extremely high sensitivity and we consider the increase in the degree of effect (hazard ratio) as reasonable.

The concentration of particulate matter increased drastically on Asian dust days. However, there are limited number of studies on effects of other air pollutants (except particulate matter) and climate factors on respiratory symptoms on Asian dust days. Although some studies regarded them as effects of modifiers, only one study considered the main effects of them to the best of our knowledge. Watanabe et al. surveyed the daily morning PEF for adult asthma patients during Asian dust. In patients with worsening of upper and/or lower respiratory tract symptoms, the daily morning PEF was significantly associated with temperature, but not with nitrogen oxides (NO_x), sulfur dioxide (SO_2), pollen or atmospheric pressure (Watanabe et al., 2011). Our study also observed that temperature had significant effects on % maxPEF for three groups. Li et al. pointed out that since ambient temperature was predicted to change worldwide due to climate change, further research was needed to examine the effect of ambient temperature on children's respiratory symptoms (Li et al., 2012). Meta-analysis observed an association between temperature drop and risk of asthma, especially in children (Cong et al., 2017). On the subject of other air pollutants, our study observed that Asian dust, O_3 and pollen caused simultaneously additive adverse effects on nasal symptoms for children without asthma. Our results suggest that respiratory symptoms on Asian dust days are varied by the climate factors and toxicity of the mixture of other air pollutants.

There are four primary strengths to this study. The first is that this study is a panel study targeting children with and without asthma, who are considered to be vulnerable to the environment and have

high sensitivity to air pollutants including Asian dust. To the authors' knowledge, there are no cases of panel studies that have investigated this and compared the degree of effect of Asian dust arrival on respiratory symptoms in children with and without asthma during the same period. The second is that this study investigated the effect of medication. There have been no previous studies that considered the effect of medication for asthma in relation to Asian dust and respiratory symptoms. In a study following adult asthma patients for four years, only 2 out of 46 subjects worsened every year upon Asian dust arrival and it was concluded that factors related to individual sensitivity played a major role (Watanabe et al., 2012). In this study, where children are the target, as a result of considering the use of long-term preventive medication when conducting the analysis, a difference was observed in children between the use and non-use of medication. Long-term preventive medication was considered to be a factor influencing individual sensitivity. Third, we evaluated the morning-evening variation of %maxPEF. The decrease of %maxPEF was observed in the morning. This result is consistent with findings that respiratory symptoms of wheeze, shortness of breath and/or cough are often worse at night or in the morning (Global Initiative for Asthma, 2020). Fourth, we investigated dose-response effect. It is not possible to investigate the Asian dust dose-response effect using a case-crossover analysis. Therefore, we used GEE analysis to investigate the dose-response relationship between Asian dust arrival amount and decrease in %maxPEF.

This study has the following limitations. The first is that the sample size for CA and CA-LTM was smaller than that for children without asthma and the confidence interval was large. In particular, for the case-crossover analysis investigating the relationship between Asian dust arrival and respiratory symptoms, the statistical power was low since both exposure and outcome were binary variables. The second is that respiratory symptoms were evaluated by a self-administered questionnaire. To ensure reliability, measurement of PEF was added as an objective indicator and %maxPEF was used as the outcome. Third, we did not consider the chemical composition in Asian dust. Recent studies have pointed out the possibility that the health effects of Asian dust may vary depending on its chemical composition (Faraji et al., 2020; Goudarzi et al., 2018; Onishi et al., 2012; Ueda et al., 2012).

5. Conclusion

A statistically significant association was found between Asian dust and decrease in %maxPEF, and there was an increase in the risk of asthma-like symptoms and nasal symptoms in CA. For children without asthma, a statistically significant association was found between Asian dust arrival and decrease in %maxPEF. On the other hand, the adverse effects in respiratory symptoms and decrease in %maxPEF were not observed in CA-LTM. This suggests the possibility that long-term preventive medication to manage asthma may suppress aggravation of respiratory symptoms due to Asian dust and may be effective for prevention.

CRedit authorship contribution statement

Hideki Hasunuma: Writing - original draft. **Ayano Takeuchi:** Formal analysis. **Rintaro Ono:** Investigation. **Yuko Amimoto:** Investigation. **Yoon Ha Hwang:** Investigation. **Itsushi Uno:** Data curation. **Atsushi Shimizu:** Data curation. **Yuji Nishiwaki:** Supervision. **Masahiro Hashizume:** Supervision. **David J. Askew:** Writing - review & editing. **Hiroshi Odajima:** Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.scitotenv.2020.141585>.

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Supplementary Material

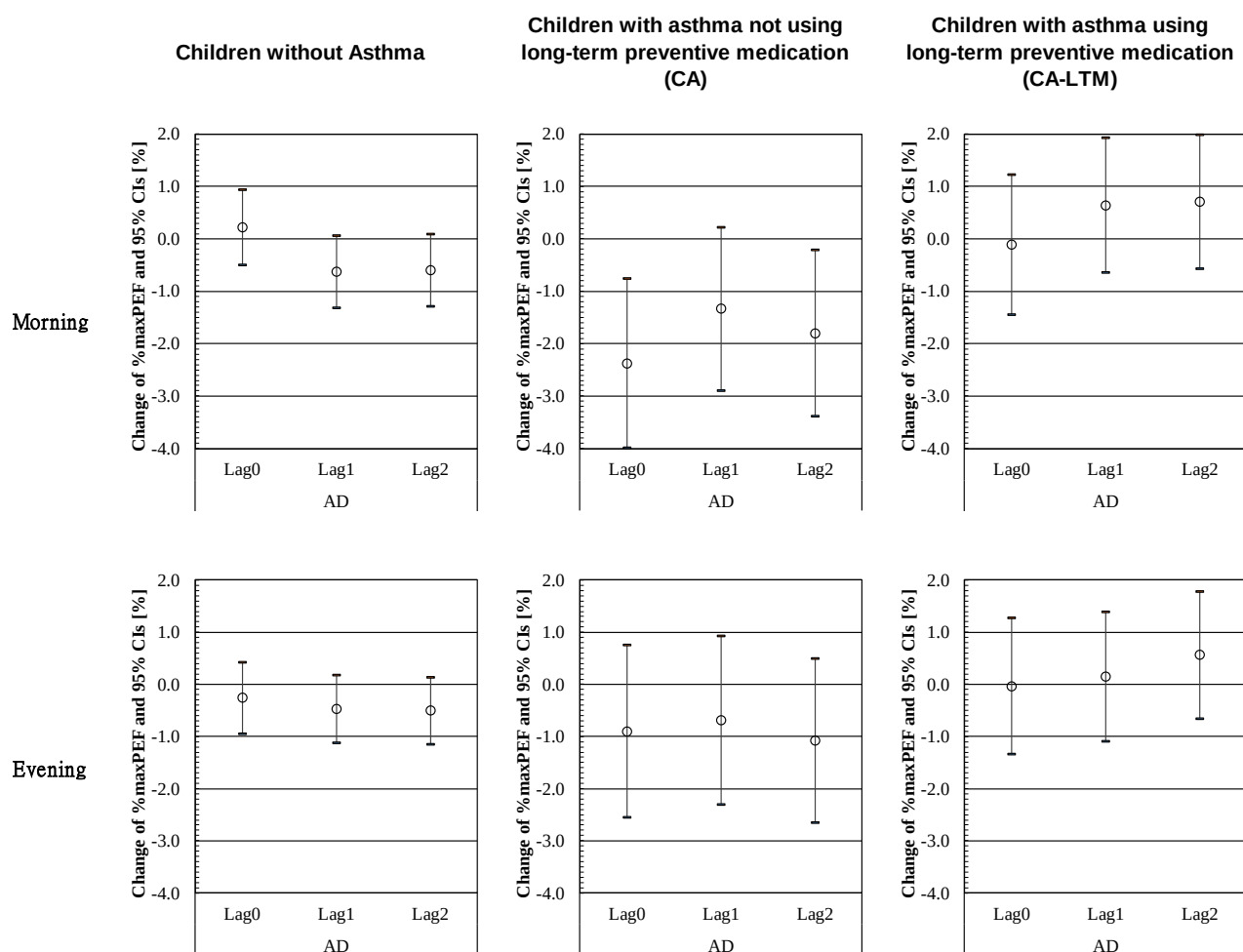


Figure S1. Association between Asian Dust and change of %maxPEF at Lag0 - Lag2 days using GEE model, adjusted for age, gender, passive smoke, temperature and humidity for morning-evening variation.

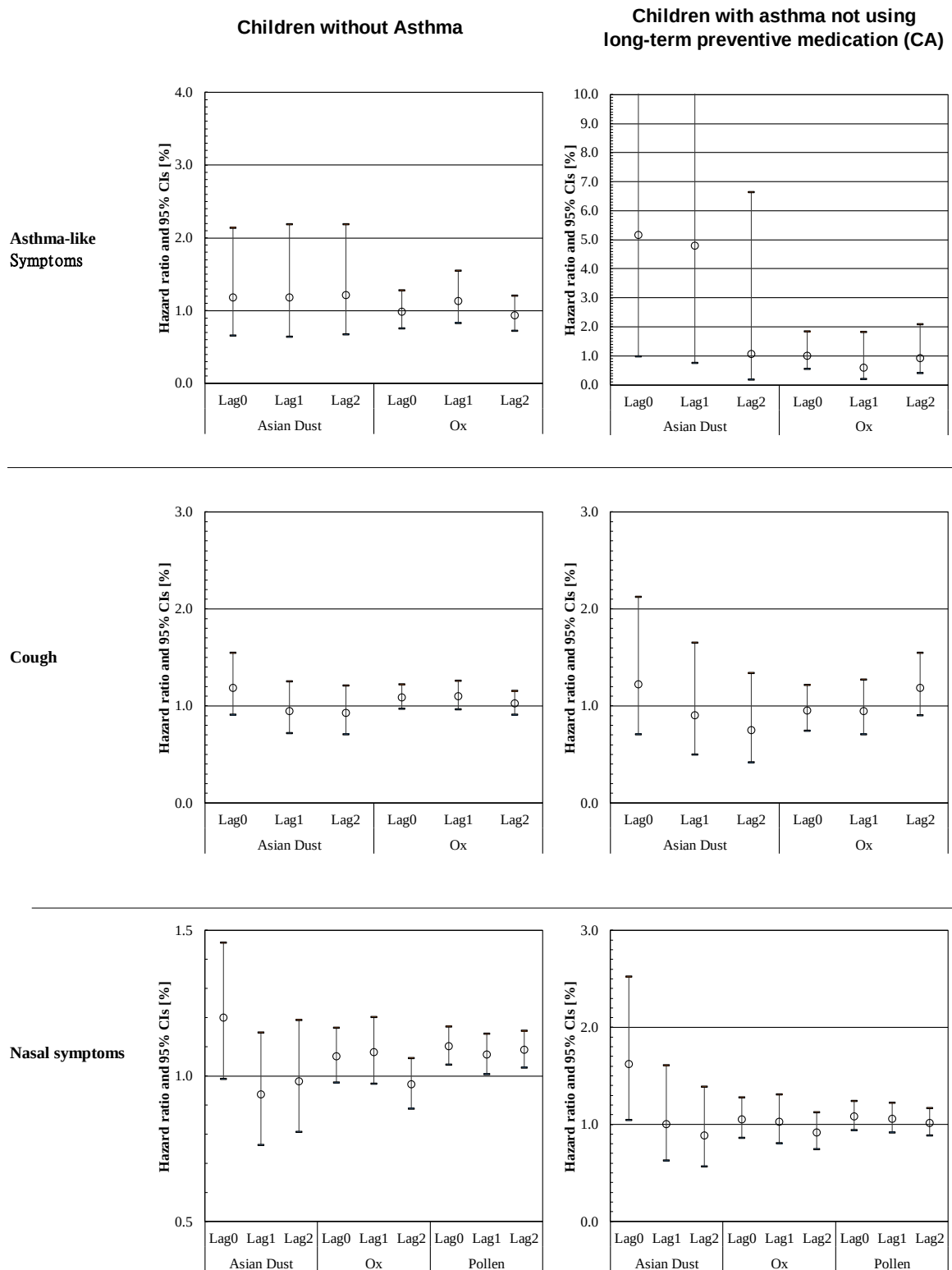


Figure S2. Association between Asian dust and respiratory symptoms at Lag0 - Lag2 days using cross-over design, adjusted for temperature drop, atmospheric pressure and photochemical oxidant (Ox). Pollen amount was added for the analysis of nasal symptoms.

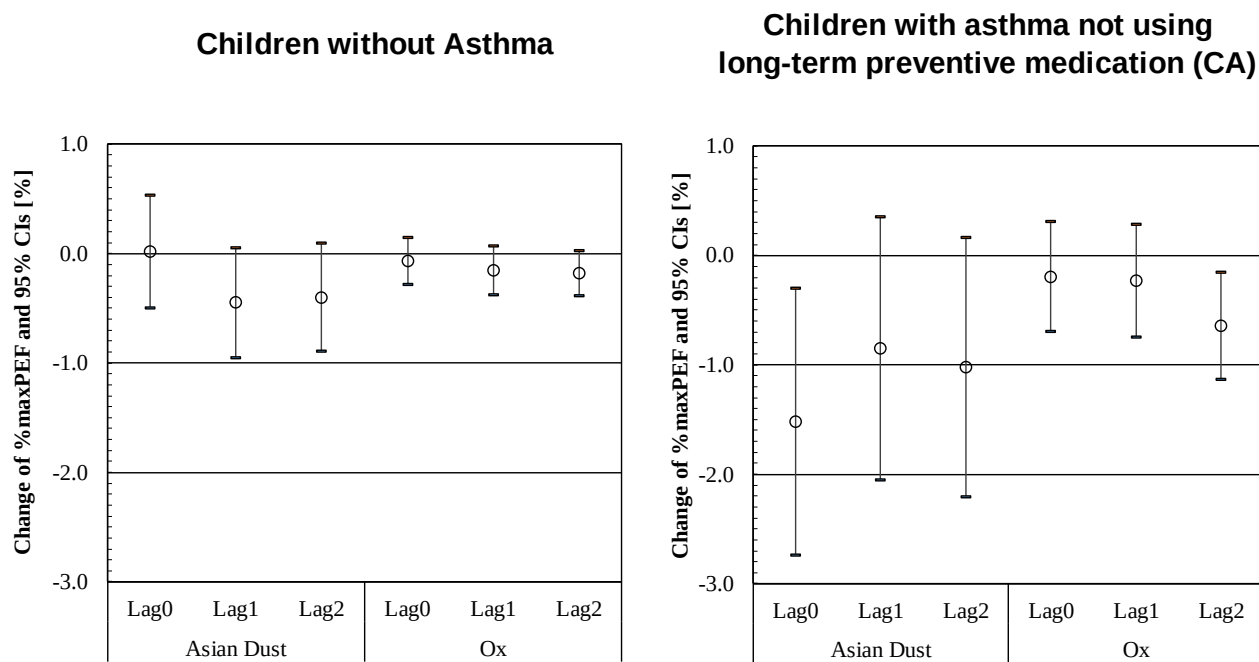


Figure S3. Association between Asian Dust and change of %maxPEF at Lag0 - Lag2 days using GEE model, adjusted for age, gender, passive smoke, temperature, humidity and photochemical oxidant (Ox).

Table S1. Association between climate factors and respiratory symptoms at lag0 day of Asian dust using case-crossover design.

		Children without Asthma			CA			CA-LTM		
		Estimation (95%CI)		p-value	Estimation (95%CI)		p-value	Estimation (95%CI)		p-value
Asthma-like symptoms	Temperature drop [per °C]	0.977	(0.890 to 1.071)	0.61	0.870	(0.662 to 1.142)	0.32	0.925	(0.803 to 1.064)	0.27
	Atmospheric pressure [per hPa]	0.991	(0.946 to 1.038)	0.71	1.080	(0.934 to 1.249)	0.30	1.015	(0.951 to 1.083)	0.66
Cough	Temperature drop [per °C]	0.997	(0.953 to 1.044)	0.91	1.032	(0.935 to 1.140)	0.53	0.978	(0.918 to 1.041)	0.48
	Atmospheric pressure [per hPa]	0.999	(0.978 to 1.021)	0.95	1.049	(1.001 to 1.099)	0.045	1.000	(0.971 to 1.030)	0.99
Nasal symptoms	Temperature drop [per °C]	1.002	(0.967 to 1.038)	0.92	0.959	(0.883 to 1.041)	0.31	0.987	(0.932 to 1.044)	0.64
	Atmospheric pressure [per hPa]	0.996	(0.978 to 1.014)	0.63	1.017	(0.975 to 1.061)	0.43	1.003	(0.975 to 1.031)	0.85

Abbreviations: CA, Children with asthma not using long-term preventive medications; CA-LTM, Children with asthma using long-term preventive medications.

Table S2. Association between climate factors, such as temperature and humidity, and change of %maxPEF at lag2 days of Asian dust using GEE model.

	Children without Asthma			CA			CA-LTM		
	Estimation	(95%CI)	p-value	Estimation	(95%CI)	p-value	Estimation	(95%CI)	p-value
Temperature [per °C]	0.218	(0.168 to 0.268)	<0.001	0.219	(0.105 to 0.333)	<0.001	0.184	(0.092 to 0.276)	<0.001
Humidity (per 1%)	0.046	(0.030 to 0.061)	<0.001	0.037	(0.001 to 0.073)	0.044	-0.007	(-0.036 to 0.022)	0.62

Abbreviations: CA, Children with asthma not using long-term preventive medications; CA-LTM, Children with asthma using long-term preventive medications; %maxPEF, the ratio of measured peak expiratory flow rate against the maximum peak expiratory flow rate of the subject.