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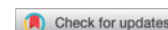
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Association between daily ambient air pollution and respiratory symptoms in children with asthma and healthy children in western Japan

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ABSTRACT

Objective: In recent years, air pollutant concentrations in Japan have decreased slightly; however, there are growing concerns about the influences of transnational air pollution on respiratory illness. We aimed to clarify the short-term association between the ambient air pollution and respiratory symptoms among children without asthma, children with asthma not using long-term medications (CA-nonLTM), and those using them (CA-LTM). **Methods:** A total of 138 children attending 2 primary schools and 71 children with asthma regularly visiting cooperating medical institutions were recruited. Study participants measured peak expiratory flow (PEF) twice a day and recorded coughing, nasal symptoms, and medication use in a diary. Predicted associations between daily air pollutant concentrations and respiratory symptoms, and PEF were evaluated using case-crossover and generalized estimate equation models. **Results:** Changes in %maxPEF per 10 ppb oxidant (Ox) increase in children without asthma, CA-nonLTM, and CA-LTM were -0.26% (95% CI: $-0.49, -0.03$), -0.51% (95% CI: $-0.89, -0.12$), and -0.20% (95% CI: $-0.42, 0.01$), respectively. The odds ratios for coughing per 10 ppb Ox increase in the Lag0 model were 1.34 (95% CI: 1.11, 1.60), 1.52 (95% CI: 1.12, 2.07), and 1.06 (95% CI: 0.93, 1.20), respectively. These suggested that the Ox concentration has graded effects on %maxPEF and coughing, in the following descending order, CA-nonLTM, children without asthma, and CA-LTM. The Ox concentration was also positively associated with nasal symptoms in children without asthma and CA-LTM. **Conclusion:** Our results suggest that using long-term medications to manage asthma may play an important role in preventing exacerbation of respiratory symptoms due to air pollution.

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Introduction

In recent years, air pollutant concentrations in Japan have decreased slightly [1]; however, there are growing concerns about the influences of transnational air pollution, arising from mainland East Asia, on respiratory illness in western Japan [2–4]. It is estimated that the contribution from foreign anthropogenic sources was greater than the domestic pollution in western Japan. The relative contribution from foreign sources in China to the annual mean fine particulate matter (PM_{2.5}) concentration was estimated to be 50–60% in western Japan [5].

Children with bronchial asthma have respiratory tract hypersensitivity, and the development of asthma symptoms is closely related with exposure to respiratory tract irritants such as air pollutants. Ambient air pollution is associated with emergency department visits and hospital admissions due to asthmatic attacks [6–9]. For the purpose of maintaining good health awareness, as well as

environmental and administrative planning, it will also be important to discern how different the effects are on healthy children compared to those with asthma. However, to date there have been very few panel studies on the association between ambient air pollution and respiratory symptoms in both healthy children and those with asthma, simultaneously [6]. To the best of our knowledge, only four such studies were reported, including Epton et al. [10], Aekplakorn et al. [11], Escamilla-Nunez et al. [12], and Jacobson et al. [13]. These studies focused on specific exhaust sources including biomass burning, power plant emissions, and traffic-related air pollution. The former three articles reported that the adverse effect of air pollutants on pulmonary health was more common in asthmatic children than in healthy children. The latter study in Brazil found that exposure to PM_{2.5} was associated with reductions in lung function in children without asthma, while no significant effect could be

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identified in the asthmatic group. Thus, the results have been contradictory and demand that further epidemiological research is needed to consider the differences between these two populations, including types of medication use, especially controllers for long-time asthma management.

Therefore, the aim of this study was to clarify the short-term association between ambient air pollution and respiratory symptoms in children with asthma and healthy children in Japan, considering the types of medication use.

Methods

Subjects

The subjects consisted of 138 children attending 2 primary schools in Fukuoka and 71 children with asthma regularly visiting cooperating medical institutions (209 children ages 6–11 years in total). After receiving informed consent from their parents, information including birth date, gender, and history of allergic diseases was obtained using a medical questionnaire. The investigation period was from April 1 to June 30, 2013 for both children attending the two primary schools and the children with asthma in cooperating medical institutions. Of the 138 children attending 2 primary 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 children with asthma and healthy children in total was 116 and 93, respectively.

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

Outcome assessment

Peak expiratory flow (PEF) was measured using a Mini-Wright Peak Flow Meter (Clement Clarke, U.S.). Before measurement, study participants received instruction and practiced using the peak flow meter. Study participants measured PEF twice a day (morning and evening) and recorded the values in a diary during the investigation period. They also recorded coughing, nasal symptoms (nasal discharge, nasal obstruction, and sneezing), and the status of medication use.

The status of medication use was classified into three categories based on their action (treating attacks, treating respiratory tract infection, and those for long-term management). The use of medications for treating attacks or treating respiratory tract infection itself was regarded

as an outcome. Since medications for long-term management may inhibit the influences of air pollution on the respiratory state, we stratified children with asthma into two groups by users or nonusers. Finally, PEF value, coughing, nasal symptoms, and use of medications for treating attacks and those for treating respiratory infection were chosen as outcomes.

Exposure assessment

Hourly air pollutant concentration data, including photochemical oxidant (Ox), nitrogen dioxide (NO₂), and PM_{2.5}, were obtained from air pollution monitoring stations, and were provided by the Atmospheric Environmental Regional Observation System or local governments [14]. Measurement methods for Ox, NO₂, and PM_{2.5} are shown in Table S1. Ox was measured by absorption photometry or ultraviolet absorption method. The latter measurement method includes ozone levels. Since oxidants are composed mainly of ozone, the ultraviolet absorption method is used to measure Ox levels in Japan. The air pollutant data used for analysis was the mean of concentrations provided by monitoring stations in the municipalities of the primary schools attended by the subjects or cooperating medical institutions. The temperature and humidity data were collected from meteorological observatories in prefectures of the primary schools attended by the subjects or cooperating medical institutions. The number of monitoring stations and the distance to the nearest monitoring station are shown in Table S2.

Statistical analysis

For the analysis of the association between the air pollutant concentrations and PEF, the generalized estimate equation (GEE) model was used. For the analysis of the association between the air pollutant concentrations and respiratory symptoms, the case-crossover model was used. To consider the influences of individual sensitivity, the subjects were classified into three groups, healthy children, children with asthma not using long-term medications (CA-nonLTM), and children with asthma using long-term medications (CA-LTM).

Using the GEE model, we estimated the change in the ratio of the PEF to the subject's maximum peak expiratory flow (%maxPEF) per 10 ppb increase in Ox concentration, per 10 ppb increase in NO₂ concentration, and per 10 µg/m³ increase in PM_{2.5} concentration in a multi-pollutant model. At first, considering the influences of the time of day on the measurement of PEF, separate analysis was performed using morning or evening data. Since similar results were found in morning and evening, we decided to pool them for analysis. The adjustment

variables included in the analysis model were age, gender, temperature, relative humidity, and living area. Ox, NO₂, and PM_{2.5} concentrations were calculated as the 24-h mean concentrations before PEF measurement. Morning and evening temperatures were those recorded at 8:00 and at 22:00, respectively. The relative humidity was used for daily mean value on the day. We took into consideration a lag effect of air pollutants up to 5 days to evaluate effects on the same day and as a result of days prior to the occurrence of the event. The variables for the living area were prefectures. In the GEE analysis, children aged 6 years were excluded because there was a possibility that accurate PEF values could not be obtained. Also, PEF values obtained by self-measurement by children have been reported to be unstable until they master the measurement technique. The PEF values on the 1st, 2nd, and 3rd days of measurement were significantly lower than the mean values on the 20th, 21st, and 22nd days of measurement (paired *t*-test procedure in SAS release 9.2 (SAS, Institute Inc., Cary, NC, USA)) (see online Table S3). Therefore, for data analysis, data on the 4th day or later were used. For GEE analysis, the GENMOD procedure in SAS release 9.2 was employed.

The association between the air pollutant concentrations and respiratory symptoms was evaluated using case-crossover analysis. The day of symptom development was used as the case, and control days were chosen on the same day of the week earlier and later in the same month. We estimated the odds ratio per 10 ppb increase in Ox concentration, per 10 ppb increase in NO₂ concentration, and per 10 µg/m³ increase in the PM_{2.5} concentration in a multi-pollutant model using logistic regression analysis with respiratory symptoms as an outcome variable, adjusted for temperature, and relative humidity. The respiratory symptoms were coughing, nasal symptoms, the use of drugs to treat attacks, and

the use of drugs to treat respiratory tract infection. For temperature and relative humidity, the mean values of the day were used. For air pollutant concentrations, the 24-h mean values before PEF measurement were used. We also took into consideration a lag effect of air pollutants up to 5 days. National holidays, including year-end and New Year holidays, were excluded from the analysis since the air pollutant concentration on these holidays tend to differ from those on ordinary days. Analysis was performed using the PHREG procedure in SAS release 9.2.

Results

Characteristics of subjects

The characteristics of the subjects are described in Table 1. The number of healthy children, CA-nonLTM and CA-LTM was 116, 36, and 57, respectively. As shown in Table 1, children without asthma exhibited lower frequencies of respiratory symptoms compared to CA-LTM. For children without asthma, frequencies of nasal symptoms, coughing, drug use for respiratory tract infection, and the use of medications for attacks were 14.6%, 6.1%, 0.9%, and 0.1%, respectively. Air pollution exposure concentrations among the three groups during the investigation period are provided in Table 2. Exposure concentrations were slightly different because of differences in observation date and living area. Correlation coefficients between air pollutants (Ox, NO₂, and PM_{2.5}) are provided in Table 3.

Association between air pollutants and peak expiratory flow (PEF)

The results of an analysis of the relationship between air pollutant concentrations and %maxPEF using the GEE model are shown in Figure 1. An increase in Ox

Table 1. Subject characteristics.

Group	Children without asthma	Children with asthma not using long-term medications (CA-nonLTM)	Children with asthma using long-term medications (CA-LTM)
Number, <i>n</i>	116	36	57
Gender			
Male, <i>n</i> (%)	53 (45.7)	21 (58.3)	35 (61.4)
Female, <i>n</i> (%)	63 (54.3)	15 (41.7)	22 (38.6)
Age (years)			
6–7, <i>n</i> (%)	25 (21.6)	8 (22.2)	21 (36.8)
8–9, <i>n</i> (%)	46 (39.7)	13 (36.1)	18 (31.6)
10–11, <i>n</i> (%)	45 (38.8)	15 (41.7)	18 (31.6)
Use of long-term medications			
Yes, <i>n</i> (%)	0 (0.0)	0 (0.0)	57 (100.0)
No, <i>n</i> (%)	116 (100.0)	36 (100.0)	0 (0.0)
Frequency of respiratory symptoms ^a			
Use of medications for attacks, %	0.1	9.5	7.3
Use of medications for respiratory tract infection, %	0.9	7.4	14.0
Coughing, %	6.1	9.1	16.6
Nasal symptoms, %	14.6	13.4	30.4

^aTotal number of days with each symptom/total number of observation days (%).

Table 2. Exposed air pollution concentration (mean $\pm$ SD) among three groups during the study period, April 1 to June 30, 2013.

		Children without asthma	Children with asthma not using long-term medications (CA-nonLTM)	Children with asthma using long-term medications (CA-LTM)
Ox	(ppb)	42.8 $\pm$ 12.3	40.4 $\pm$ 12.8	36.5 $\pm$ 12.5
NO ₂	(ppb)	13.4 $\pm$ 4.5	10.5 $\pm$ 6.4	10.9 $\pm$ 5.2
PM _{2.5}	(μ g/m ³)	22.9 $\pm$ 13.0	21.4 $\pm$ 13.6	20.5 $\pm$ 12.7
Observation days	(days per person)	66.3	55.9	66.9

Note. Abbreviations: Ox, photochemical oxidant; NO₂, nitrogen dioxide; PM_{2.5}, fine particulate matter; SD, standard deviation.

Table 3. Correlation coefficients between air pollutants (Ox, NO₂, and PM_{2.5}).

	Ox	NO ₂	PM _{2.5}
Ox	—	0.09	0.35
NO ₂	—	—	0.49
PM _{2.5}	—	—	—

Note. Abbreviations: Ox, photochemical oxidant; NO₂, nitrogen dioxide; PM_{2.5}, fine particulate matter.

concentration was found to be significantly associated with a reduction in %maxPEF for both children without asthma and CA-nonLTM. However, no association was found for NO₂ or PM_{2.5}.

In children without asthma, the changes in %maxPEF for the Lag3 model were -0.26% (95% CI: $-0.49, -0.03$) per 10 ppb increase in the Ox concentration, showing a

significant decrease. With the other lag models, no significant association was observed.

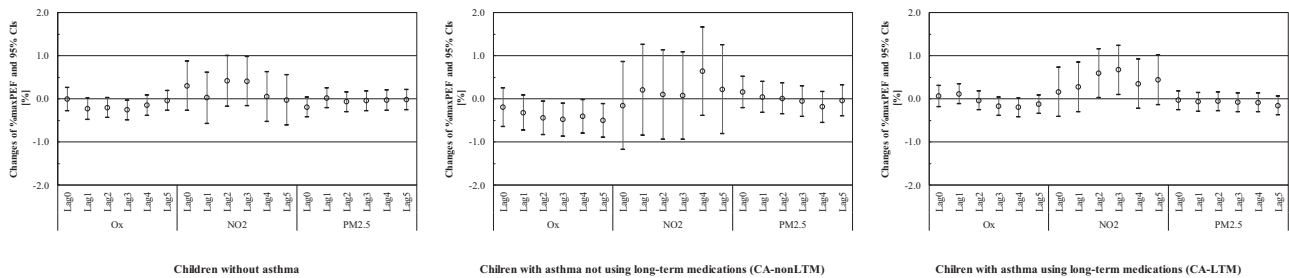
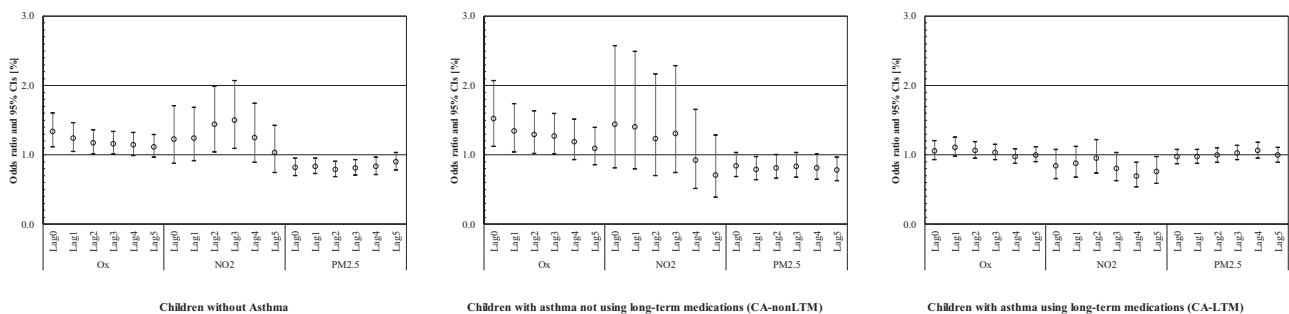
In the CA-nonLTM group, observed reductions in respiratory function were found to represent a significant decrease in %maxPEF by the Lag2 to Lag5 models. The greatest decline in %maxPEF was -0.51% (95% CI: $-0.89, -0.12$) at the Lag5 model. The decrease in %maxPEF of CA-nonLTM was greater than that of children without asthma.

In CA-LTM, increases in NO₂ concentrations were significantly associated with increases in %maxPEF. This result contradicts the hypothesis that air pollution adversely affects respiratory health. As for Ox, the changes in %maxPEF for the Lag4 model were -0.20% (95% CI: $-0.42, 0.01$) per 10 ppb increase in the Ox concentration. Thus, the adverse effect of Ox on %maxPEF was found among three groups, though the effect sizes are different. The greatest decrease in %maxPEF was found in children with asthma who did not use controllers (CA-nonLTM).

Association between air pollutants and respiratory symptoms

The results of our analysis of the association between air pollutants and coughing and nasal symptoms using case-crossover analysis are presented in Figures 2 and 3.

As shown in Figure 2, Ox concentration was positively associated with coughing in the Lag0 to Lag3 models in

**Figure 1.** Association between air pollutant concentrations and %maxPEF at Lag 0 to Lag 5 days using the generalized estimated equation model, adjusted for age, gender, temperature, relative humidity, and living area. Abbreviations: %maxPEF, the ratio of peak expiratory flow to the subject's maximum peak expiratory flow; Ox, photochemical oxidants; NO₂, nitrogen dioxide; PM_{2.5}, fine particulate matter.**Figure 2.** Association between air pollutant concentration and coughing at Lag 0 to Lag 5 days using the case-crossover model, adjusted for temperature and relative humidity. Abbreviations: Ox, photochemical oxidants; NO₂, nitrogen dioxide; PM_{2.5}, fine particulate matter.

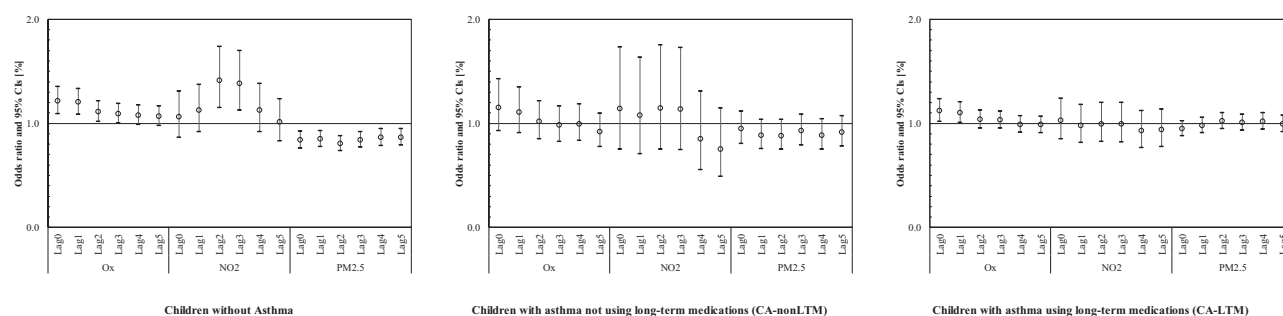


Figure 3. Association between air pollutant concentration and nasal symptoms at Lag 0 to Lag 5 days using the case-crossover model, adjusted for temperature and relative humidity. Abbreviations: Ox, photochemical oxidants; NO₂, nitrogen dioxide; PM_{2.5}, fine particulate matter.

healthy children and CA-nonLTM. The odds ratio for coughing per 10 ppb increase in the Ox concentration in healthy children, CA-nonLTM and CA-LTM in the Lag0 model were 1.34 (95% CI: 1.11, 1.60), 1.52 (95% CI: 1.12, 2.07), and 1.06 (95% CI: 0.93, 1.20) respectively. NO₂ concentrations were positively associated with coughing in healthy children by the Lag2 and Lag3 models.

As shown in Figure 3, Ox concentrations were positively associated with nasal symptoms in healthy children and CA-LTM. The associations were not statistically significant in CA-nonLTM. The odds ratio for coughing per 10 ppb increase in the Ox concentration in healthy children, CA-nonLTM, and CA-LTM in the Lag0 model were 1.22 (95% CI: 1.09, 1.35), 1.15 (95% CI: 0.93, 1.43), and 1.12 (95% CI: 1.02, 1.24), respectively. Odds ratios are approximately 1.1–1.2 among three groups. The limited sample size may be considered a factor in the failure to detect a significant relationship in CA-nonLTM case. NO₂ concentrations were positively associated with nasal symptoms in healthy children in Lag2 and Lag3 models.

Regarding the use of medications for attacks, no significant positive association was found in either CA-nonLTM or CA-LTM. For medication use for respiratory tract infection, Ox and NO₂ concentrations were positively associated only in healthy children (data not shown).

Discussion

In this study, the effects of ambient air pollutants on respiratory values including %maxPEF and respiratory symptoms were analyzed in children with and without asthma. Ox concentrations were found to be positively associated with diminished breathing performance as indicated by %maxPEF, coughing, and nasal symptoms for both children with and without asthma. For NO₂ concentrations, a significant positive association was found between %maxPEF, coughing, and nasal symptoms only in children without asthma. Meanwhile, no significant positive association was identified between PM_{2.5} concentrations and

any of the deteriorating respiratory symptoms. Our study also found a lag effect of Ox and NO₂. A possible explanation for our findings of lag effect on respiratory symptoms is that Ox and NO₂ possess strong oxidizing properties.

Li et al. [6] reviewed more than 30 relevant panel studies on the effects of air pollution on children's lung function and respiratory symptoms. They reported that NO₂ and particulate matter had more significant effects in general, whereas a few studies indicated that ozone concentrations interacted with temperature and sometimes seemed to be a protective factor for children's respiratory health [15]. While our results differed from this summary report regarding the activity of ozone, our findings are consistent with the results of several other previous studies. A recent analysis by the U.S. Environmental Protection Agency concluded that there was consistent evidence of a causal relationship between short-term exposure to ozone and respiratory health effects [16]. Several studies have also suggested that ozone exposure decreased lung function in children [17–20] and increased the occurrence of respiratory symptoms [4,19,21]. For instance, Mortimer et al. [18] evaluated the effects of several air pollutants (ozone, sulfur dioxide, NO₂, and particles with a 50% cut-off aerodynamic diameter of 10 μm (PM₁₀)) on PEF in 846 children with asthma in 8 urban areas of the United States. Only ozone was found to be associated with declines in PEF. Yamazaki et al. [4] conducted a case-crossover-designed study in Himeji City, Japan, involving 112 subjects, aged 0–80 years, who visited a clinic due to an asthma attack in 2013 (examining the same period or episode of transnational air pollution as our study). They noted a positive relation between ozone levels and primary care visits due to asthma attack; however, no association was found with PM_{2.5}. Our findings also support the existence of an association between Ox concentrations and respiratory effects.

An important aspect of understanding air pollutant effects is the comparison of asthmatics and children without asthma, and the differences in their sensitivities.

Li et al. [6] reported that positive associations between air pollutants and pulmonary symptoms were found more in children with asthma than in healthy subjects. Our study found more detailed results by stratifying children with asthma by non-users (CA-nonLTM) or users (CA-LTM) of long-term medications. Our results suggest that air pollution has graded effects, in the following order, on CA-nonLTM, healthy children and CA-LTM. These results may describe the successful use of medications to manage asthma, as well as an important role for controllers in preventing exacerbation of respiratory symptoms due to air pollution. In fact, Japanese pediatric guidelines for the treatment and management of bronchial asthma [22] recommend the use of controllers for long-time management, prevention and early intervention.

There are two primary strengths to this study. First, we conducted a panel study of both asthmatics and children without asthma during the same period. Subjects were recruited from primary schools and cooperating medical institutions. Differences in the short-term influences of air pollutant concentrations in Japan between the populations could be carefully clarified. By comparing the results between each group, it was also possible to raise the reliability of the analysis of the relationship between ambient air pollution and respiratory symptoms. Second, we took medication use into consideration in this study. Detailed information on medication use was evaluated, including medications for attacks, respiratory tract infection, and controllers for long-term management. There are a few similar studies using medication use as an outcome. In our study, a significant association with the use of medications for respiratory tract infection in children without asthma was found. Gent et al. [23] reported that, for children with asthma, increased risk of daily symptoms and medication use was associated with daily traffic-related fine particle sources. Klot et al. [24] reported a significant association between inhaled corticosteroid use and the $PM_{2.5}$ concentration on the same day [odds ratio per interquartile range increase ($28 \mu g/m^3$), 1.10] in adults. $PM_{2.5}$ concentration was not associated with beta-2-agonist use, wheezing, shortness of breath, phlegm, or cough. The results of our study on children with asthma as well as those of the studies by Gent and Klot et al. [23,24] suggest that air pollution may effect medication use, particularly that which has direct effects on respiratory symptoms. To evaluate the short-term influences of air pollutant concentrations, the information on medication use is thought to be indispensable, especially in children with respiratory diseases.

This study has the following limitations. First, we increased the number of cooperating medical institutions to increase the number of subjects with asthma. As a result, the investigation area became larger, and additional differences in regional characteristics such as climate and

lifestyle habits were introduced. There is a possibility that adjustment for such regional characteristics was inadequate. Second, there is also a possibility that differences in individual adherence to a daily schedule of medication use to manage asthma, which is considered to be associated with PEF and the development of respiratory symptoms, affected the association between the air pollutant concentrations and the PEF or respiratory symptoms. Third, our study differed from previous studies in that information on $PM_{2.5}$ concentrations (including forecast) as an exposure parameter was reported to the public daily through newspapers, TV, and the Internet during the investigation period. In particular, on days showing a high $PM_{2.5}$ concentration, children with asthma who are considered to be sensitive to $PM_{2.5}$ may have taken preventive measures (behavioral change), which might have affected the association between the air pollution and PEF value or symptoms in our study. For instance, Lee et al. reported that, in response to the dust storm warning system in Taipei, the occurrence of Asian dust storms now have a protective effects on mortality because people are more cautious [25]. In observational studies on the influences of air pollution on health in the future, consideration should be given to days when a warning is issued and subjects' preventive behavior, both as confounding factors. With respect to our findings of an inverse association between NO_2 and %maxPEF in CA-LTM, we speculate that it resulted from these proactive actions, and high correlation between NO_2 and $PM_{2.5}$ ($r = 0.49$) that might possibly cause multicollinearity in multi-pollutant models. Fourth, we did not consider allergic predisposition. If subjects had allergies, they might react sensitively to the air pollutants. It might be a bias to the results. However, we did not have information on serum IgE values.

Conclusions

Ox concentrations were found to have a significant positive association with %maxPEF, coughing, and nasal symptoms for both children with and without asthma. Positive associations were found to be the greatest in children with asthma who did not use controllers, followed in order by healthy subjects and children with asthma who do use controllers. $PM_{2.5}$ concentrations were not significantly associated with any symptoms. Our results suggest that using medications to manage asthma may play an important role in preventing exacerbation of respiratory symptoms due to air pollution.

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Declaration of interest

The authors have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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