



Comparison of diverse estimation methods for personal exposure to air pollutants and associations with allergic symptoms: The Allergy & Gene-Environment Link (ANGEL) study

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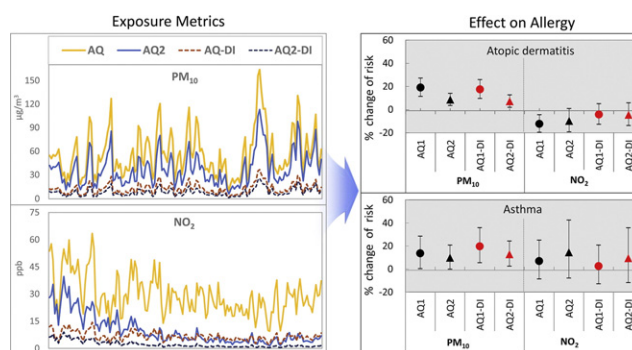
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HIGHLIGHTS

- A new method for estimating personal exposure to air pollutants was proposed.
- Personal exposure of air pollution showed different spatial and temporal distribution from ambient concentration.
- The effects of air pollution on allergic symptoms varied by exposure metric and disease.
- The effect sizes of PM₁₀ exposure on asthma symptoms can be greater in metrics that considered inhalation capacity.

GRAPHICAL ABSTRACT



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ABSTRACT

We estimated the exposure to ambient air pollutants and analyzed the associations with allergic diseases. We enrolled 177 children with atopic dermatitis (AD) and 70 asthmatic adults living in Seoul Metropolitan Area, Korea, and followed for 17 months between August 2013 and December 2014. Parents or patients recorded symptom scores on a daily basis. Exposure to particulate matter with a diameter <10 μm (PM₁₀) and nitrogen dioxide (NO₂) was estimated in four different ways in each individual, using the AQ1 (measurements from the nearest air quality monitoring station to residential houses), AQ2 (measurements modified from AQ1 with the indoor level of air pollutants and time activity of each individual), AQ1-DI, and AQ2-DI (measurements modified from

Abbreviations: AD, atopic dermatitis; ADI, average daily intake; AQMS, air quality monitoring system; FEV₁, forced expiratory volume in 1 s; GIS, geographic information system; GLMM, generalized linear mixed model; I/O ratio, indoor-to-outdoor pollutant concentration ratio; IQR, interquartile range; NO₂, nitrogen dioxide; PM₁₀, particulate matter with a diameter <10 μm; SCORAD, SCORing Atopic Dermatitis.

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AQ1 and AQ2, respectively, with daily inhalation intakes of air pollutants). A generalized linear mixed model (GLMM) was used to analyze the associations between exposure metrics and clinical symptoms after adjusting for ambient temperature and humidity, age, season, gender, and time trend. The exposure metrics for PM₁₀ and NO₂ showed different distributions. Symptoms of AD and asthma were positively associated with exposure to PM₁₀, but not NO₂, in all exposure metrics. The effect size of PM₁₀ exposure on asthma symptoms was slightly greater in metrics with inhalation capacity (AQ-DIs) than in those without (AQs). This pattern was not observed in AD. Exposure to PM₁₀ is associated with symptom aggravation in childhood AD and adult asthma. Different exposure estimates may be used to evaluate the impact of air pollution on different allergic diseases.

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1. Introduction

Assessment of exposure to air pollution is a critical part of evaluating the effect of air pollution on public health. Recently, there has been increasing interest in estimating the health effects of air pollution based on accurately quantified exposure of the population (Baxter et al., 2013; Mannhardt et al., 2013; Miller et al., 2007; Molter et al., 2013; Ozkaynak et al., 2013; Wang et al., 2015). Many epidemiologic studies have used measurements from air quality monitoring systems (AQMSs) to characterize exposure to ambient air pollutants at a population level (Baxter et al., 2013). Some studies used proximity-based assessments, statistical interpolation including land-use regression, and air quality modeling from AQMS measurements (Baxter et al., 2013; Bravo et al., 2012; Jerrett et al., 2005). However, measurements from outdoor monitors do not adequately reflect a population's behavior or the spatial variation in pollutant concentrations (Payne-Sturges et al., 2004). The physical characteristics of individuals, such as inhalation rate, may also vary when investigating the health effect of air pollution (e.g., effects on respiratory diseases). Few studies have examined the exposure level of air pollutants by considering the effect of indoor levels, individual behaviors, and physical characteristics with respect to their health. Multiple approaches were recently used to evaluate the impact of air pollution on health (Baxter et al., 2013; Wang et al., 2015). In several studies, passive samplers were used to estimate personal exposure to air pollutants. For example, Brauer and Brook (1997) assessed ozone exposure using a passive sampler and then analyzed the association of ozone with lung function after considering the time-activity pattern of subjects. However, a passive sampler has limited temporal resolution and does not operate continuously throughout the year. Therefore, alternative methods for estimating personal exposure in a large population with high temporal resolution must be developed.

Atopic dermatitis (AD) and asthma are very common disorders frequently influenced by environmental factors. The prevalence of AD in children aged 6 to 7 years and 13 to 14 years is increasing in both developing and developed countries, according to Phases One and Three of the International Study of Asthma and Allergies in Childhood (Ahn, 2016; Williams et al., 2008). Although the reason for this is not clearly understood, air pollution may be involved in the development or aggravation of AD (Ahn, 2014). The prevalence of asthma has also been increasing in many countries with low prevalence (Asher et al., 2006). Air pollution may act as a causative factor in asthma development (Clark et al., 2010; Jacquemin et al., 2015; Pearce et al., 2007), but it is controversial whether air pollution played a major role in the recent increase in asthma prevalence (Platts-Mills, 2015). A recent study by Wang et al. (2015) examined the effect of air pollution on lung function in children by comparing exposure estimates between land use regression and dispersion exposure modeling approaches. However, neither allergic symptoms as health outcomes nor exposure estimates considering human behavior and physical characteristics was evaluated in that study. To better understand the effect of air pollution on allergic diseases, various metrics of exposure to air pollutants should be explored.

We sought to evaluate various estimates of exposure to air pollution considering human behavior and daily intake at an individual level in patients with childhood AD and adult asthma. We also investigated

the clinical effect of exposure to air pollutants by comparing effect sizes among different exposure metrics.

2. Materials and methods

2.1. Study design

The Allergy & Gene-Environment Link (ANGEL) study was performed to investigate the impact of air pollution on allergic diseases. This prospective study was designed as a panel study consisting of three parts: exposure assessment, clinical assessment of children with AD and asthmatic adults, and association analyses (Fig. 1). We first assessed four exposure estimates for particulate matter with an aerodynamic diameter of 10 µm or less (PM₁₀) and nitrogen dioxide (NO₂) based on AQMS measurements in the Seoul Metropolitan Area, Korea (Fig. 2). AQ1 was determined by simple distribution of AQMS measurements from the nearest station to each individual's home address. AQ2 was calculated by modifying AQ1 with the indoor level and time activity of each participant, the time-weighted-average personal exposure. AQ1-DI and AQ2-DI were measurements modified from AQ1 and AQ2, respectively, with daily inhalation intake of air pollutants. In the present study, we collected allergic symptom data on a daily basis from children with AD and asthmatic adults. The associations between estimates of air pollutant exposure and allergic symptoms were analyzed, as well as whether the associations differ depending on exposure metrics.

2.2. Study population and allergic symptoms

In the present study, 177 children with AD aged under 6 years (110 boys and 67 girls) and 70 adults with asthma aged over 18 years (21 males and 49 females) living in the Seoul Metropolitan Area, Korea, were enrolled and followed for 17 months between August 2013 and December 2014. A diagnosis of AD was determined according to the Hanifin and Rajka criteria (Hanifin and Rajka, 1980). AD severity was assessed using SCORing Atopic Dermatitis (SCORAD) ranging from 0 to 103 (European Task Force on Atopic Dermatitis, 1993). Asthma was diagnosed by a physician based on clinical symptoms and positive airway hyper-responsiveness. Airway hyper-responsiveness was confirmed by either bronchodilator reversibility of at least 12% in forced expiratory volume in 1 s (FEV₁) or provocation concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) <25 mg/mL.

In children with AD, total IgE and specific IgE against egg white, cow's milk, soybean, wheat and peanut in the peripheral blood was measured by ImmunoCAP (ThermoFisher Scientific Inc., Waltham, MA, USA) and considered positive when the level was 0.35 kU/L or above. In asthmatic adults, skin prick tests were performed to detect specific IgE against common inhalant allergens including *Dermatophagoides pteronyssinus*, *D. farinae*, tree pollen mixture, grass pollen mixture, weed pollen mixture, cockroach, cat, dog, *Alternaria alternata*, and *Aspergillus fumigatus* (Lofarma, Milan, Italy). Histamine was used as a positive control and normal saline was used as a negative control. A positive response to the skin prick test was determined when wheal size was ≥ 3 mm and controls showed adequate reactions.

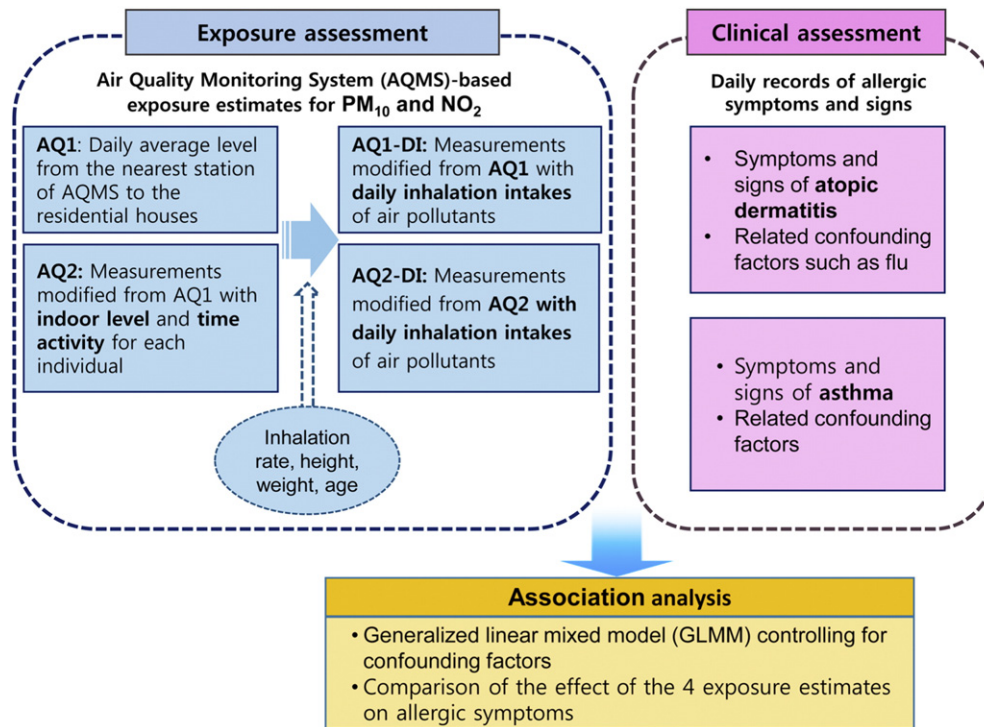


Fig. 1. Study design. AD, atopic dermatitis; AQMS, air quality monitoring system; SCORAD, SCORing Atopic Dermatitis.

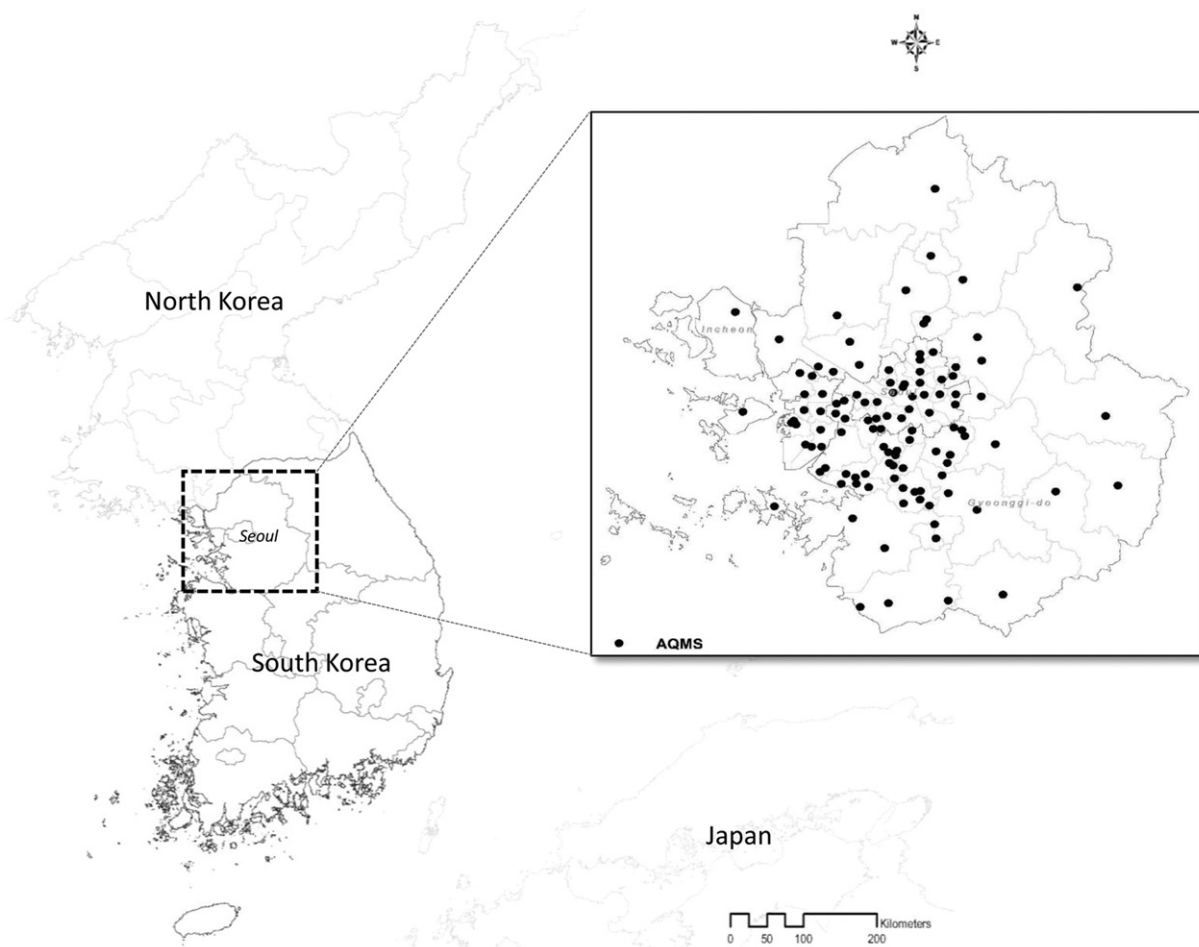


Fig. 2. Study area. Black dots indicate location of air quality monitoring system (AQMS) stations.

Patients or their parents were instructed to record symptom scores on a daily basis. For AD, a symptom diary was used to describe the extent of itching and sleep disturbance and the degree of erythema, dryness, oozing, and edema on a scale of 0 to 4. The presence of AD symptoms in daily records was defined as follows. A symptom score of 2 or more was given for the sum of itching and sleep disturbance scores plus at least two symptoms among erythema, dryness, edema, or oozing on the same day. Chest discomfort, cough at night, wheezing, and awakening at night were recorded for asthma, and the presence of at least 1 symptom was considered positive.

Written informed consent was obtained from participants and parents or guardians of all participating children. Study protocols were reviewed and approved by the Institutional Review Board (IRB) at Samsung Medical Center (IRB No: 2013-05-009).

2.3. Exposure assessment

Hourly concentrations of PM₁₀ and NO₂ were obtained from the National Institute of Environmental Research where AQMS data were produced. There were 96 monitoring stations in the Seoul Metropolitan area, covering 11,704 km² and approximately 25 million people in 2014. From hourly data, the daily 24-hour average values of PM₁₀ and NO₂ were calculated. PM₁₀ and NO₂ were not only selected because they are principal air pollutants in the study area, but also because their indoor levels are becoming more concerning (Lee et al., 2016a; Lee et al., 2016b). Daily ambient temperature and relative humidity data were obtained from the Korean Meteorological Administration (KMA) and were included in health effect models as confounding factors.

From AQMS-based measurements, 4 different exposure assessments were conducted for AD and asthma patients at an individual level as follows;

- AQ1: AQ1 included the daily average levels of ambient PM₁₀ and NO₂ measurements. Each patient was assumed to remain outdoors for 24 h and be exposed to the AQ1 levels of PM₁₀ and NO₂. After the distance from the residence to the AQMS station was calculated using geographic information system (GIS) mapping, AQ1 was determined by matching ambient PM₁₀ and NO₂ concentrations from the nearest station.
- AQ2: Indoor concentrations and time spent indoors were taken into account when AQ2 was estimated from AQ1. Concentrations of PM₁₀ and NO₂ while staying outdoors were the same as with AQ1, but concentrations of PM₁₀ and NO₂ while staying indoors were calculated with an indoor-to-outdoor pollutant concentration ratio (I/O ratio) and the time activity pattern. The process for estimating AQ2 was as below.

I/O ratio: Among 177 children with AD, 16 parents agreed to measure indoor and outdoor levels of PM₁₀ and 12 parents agreed to measure indoor and outdoor levels of NO₂ at their homes for 48 h. All indoor activities, information regarding housing and residents, and meteorological parameters from the KMA were also collected as predictor candidates. Correlation analysis and multi-step multivariate linear regression analysis was performed to develop a model for the I/O ratio of PM₁₀ and NO₂. The resulting models for PM₁₀ and NO₂ are given by

$$\text{I/O ratio for PM}_{10} = 0.0136 \cdot T - 0.00721 \cdot FL + 0.621 \quad (1)$$

$$\text{I/O ratio for NO}_2 = -0.0451 \cdot T + 1.1750 \quad (2)$$

where T and FL are temperature and floor level, respectively.

Coefficients of determination (R²) of the regression models for PM₁₀ and NO₂ were 0.57 and 0.29, respectively. Based on Eqs. (1) and (2), the indoor PM₁₀ and NO₂ concentrations of each patient's house could be

estimated by multiplying the predicted I/O ratio and outdoor concentrations obtained from AQMS (More details in Lee et al. 2016a; Lee et al., 2016b).

Time-activity: To obtain time spent indoors for each participant, a time-activity diary was given to participants. Diaries were filled in for weekdays, Saturdays, and Sundays and were used as representative patterns for the study period. Among enrolled patients, diaries were collected for 151 CE and 55 asthmatic patients. Based on the time-location data, time spent indoors and outdoors was calculated for each individual.

With time spent indoors and air pollutant concentrations driven from the I/O ratio and ambient concentration, the time-weighted exposure estimate (AQ2) was calculated. This considered both time spent indoors and indoor concentration.

- AQ1-DI: Daily inhalation intake of PM₁₀ and NO₂ was estimated at an individual level. Daily intake was calculated from the AQ1 exposure estimates based on inhalation rate, weight, height, age, and gender for each patient.
- AQ2-DI: AQ2-DI considered the daily inhalation intake of PM₁₀ and NO₂ based on AQ2 exposure estimates. This means that AQ2-DI considered time spent indoors, indoor concentration, and the physical status (including inhalation capacity) of each patient.

Daily inhalation intake was estimated as follows. To assess average daily inhalation intake (ADI) for the AQ1-DI and AQ2-DI estimates, the long-term inhalation rates for the Korean population driven from two previous studies on exposure factors were used; one for Korean children (Korea National Institute of Environmental Research, 2014) and the other for Korean adults (Korea Ministry of Environment, 2007). Exposure factors were calculated according to gender and age, and the long-term inhalation rates were based on more than 30 days' repeated exposure measurements (US Environmental Protection Agency, 2011). The equation for the individual ADI of air pollutants is given by

$$\text{ADI} = \frac{C \times \text{IR} \times \text{ED}}{\text{BW} \times \text{AT}} \quad (3)$$

where ADI is average daily inhalation intake at an individual level (μg/kg-day in PM₁₀ and μL/kg-day in NO₂), C is the concentration of air pollutant from AQ1 or AQ2 data sets (PM₁₀, μg/m³; NO₂, ppb), IR is the daily inhalation rate by age and gender (m³/day), ED is exposure duration to air (1 day), BW is body weight of each subject (kg), and AT is time period over average dose (1 day).

Paired *t*-tests with Bonferroni correction was applied to investigate the differences between mean values of the distributions estimated by 4 different models. Spearman rank correlation coefficient was used to examine changes in the order of exposure metrics.

2.4. Effect of air pollutants on allergic symptoms

Considering that repeated measurement of allergic symptoms provide longitudinal data with a binomial distribution, the generalized linear mixed model (GLMM) was adopted to estimate effects of PM₁₀ and NO₂ on allergic symptoms. To account for serial correlation among repeated measurements, the GLMM models included random effects for each subject. Multipollutant models including PM₁₀ and NO₂ in the same model were used to consider the possibility of complex interactions among pollutants in producing effects on allergic symptoms (Tolbert et al., 2007; Wang et al., 2015). Potential confounding factors such as age, gender, season, day of the week, temperature, and relative humidity were controlled. We also controlled long-term trend. For effects on AD symptoms, SCORAD at enrollment and the presence of

fever as a proxy of infection were also controlled. To consider the delayed effect of air pollutants on the presence of allergic symptoms, the effect of lagged predictor variables for PM₁₀ and NO₂ were analyzed, including unlagged (LAG0), lagged by 1, 2, and 3 days (LAG1, LAG2, and LAG3), and effect of the moving average of 4 days throughout the 3 previous days and the current day (LAG0–3). All results were expressed as percent change with 95% confidence intervals (CIs) of symptoms per increments of interquartile range (IQR) of PM₁₀ and NO₂ exposure.

The model specifications are as follows:

$$\begin{aligned} \text{logitE}(Y) = & \beta_0 + \beta_1(\text{PM}_{10}) + \beta_2(\text{NO}_2) + \beta_3(\text{temp}) + \beta_4(\text{RH}) \\ & + \beta_5(\text{season}) + \beta_6(\text{age}) + \beta_7(\text{sex}) + \beta_8(\text{DOW}) \\ & + \beta_9(\text{time}) + \gamma(\text{subject}) \end{aligned} \quad (4)$$

where $E(Y)$ is expected expression of AD and asthmatic symptoms, *temp* is daily mean temperature, *RH* is relative humidity, *DOW* is day of the week, *time* is date of Gregorian calendar, and γ is random effect for subjects. There are four seasons in Korea; that is, spring including March, April, and May, summer including June, July, and August, fall including September, October, and November, and winter including December, January, and February. In AD models, SCORAD at enrollment and fever terms were also included. Smoking was added in the asthma models.

Assuming that PM₁₀ and NO₂ are independent risk factors for aggravation of allergic symptoms, two-pollutant models were adopted to determine which pollutant is the better predictor of health outcomes (Tolbert et al., 2007). For consistent comparisons of the effect of the 4 exposure metrics on allergic symptoms, days with missing measurements for any of the pollutants and weather were excluded.

All procedures were conducted using SAS9.3 (SAS Institute, Cary, NC) and R version 3.0.0 (Comprehensive R Archive Network: <http://cran.r-project.org>). Among R packages, the “lme4” package (version 3.1–2) was used for GLMM model fitting. All tests were two-sided, and an alpha level of <0.05 was considered significant.

3. Results

3.1. Subject characteristics and data summary

From 177 patients with AD and 70 patients with asthma, the records of 29,683 and 13,989 person-days were obtained to produce data sets for AD and asthma, respectively. During the study period, 170 days (SD = 124 days) for AD symptoms and 199 days (SD = 123 days) for asthma were reported on the average. Average ages were 2.0 years (SD = 1.6 years) in AD and 46.0 years (SD = 11.3 years) in asthma patients. In AD patients, boys were more than girls, whereas, female patients were more than male in asthma patients. The presence of AD symptoms was found in 44.8% of records, and the presence of asthma symptoms was found in 14.4% of records. Average total IgE levels in AD and asthma patients were 366.4 kU/L (standard deviation (SD) = 801.2 kU/L) and 405.3 kU/L (SD = 578.5 kU/L), respectively.

3.2. Air pollution exposure assessment

The average distances between AQMS stations and patient residences were 1.97 km (SD = 1.22 km) for AD patients and 2.23 km (SD = 1.50 km) for asthma patients. Time spent indoors for children with AD was approximately 22.63 h (SD = 1.20 h) during weekdays and 21.99 h (SD = 1.42 h) during weekends, while asthmatic adults stayed indoors for 21.12 h (SD = 1.14 h) during weekdays and 21.13 h (SD = 1.31 h) during weekends. AD children stayed indoors for 93.0% of the day and asthmatic adults stayed indoors for 88.1% of the day, on average. I/O ratios for PM₁₀ and NO₂ in AD children were 0.77 (SD = 0.08) and 0.50 (SD = 0.23), respectively. I/O ratios were 0.72 (SD = 0.10) for PM₁₀ and 0.65 (SD = 0.27) for NO₂ in asthmatic adults. More details regarding time activity pattern and I/O ratio are

presented in the Supplementary Material (Table S1). Inhalation rates used to estimate AQ-DIs are also available in the Supplementary Material (Table S2).

As shown in Table 2, the exposure estimates of PM₁₀ and NO₂ varied by exposure metrics. Overall, the exposure levels for PM₁₀ and NO₂ considering indoor levels (AQ2) were lower than those of ambient levels (AQ1). Daily intake of PM₁₀ and NO₂ (AQ-DIs) in children with AD was 3 to 4 times higher than that for asthmatic adults, reflecting a difference in body weight between adults and children (Table 1). Paired *t*-test with Bonferroni correction showed that the mean values of any pair from the four exposure metrics of PM₁₀ and NO₂ were different from each other with statistical significance (*P*-values < 0.0001).

Fig. 3(A) and (B) show temporal variations of four different exposure metrics for PM₁₀ and NO₂ in the study period. AQ-DIs showed different temporal variations from AQs, particularly in NO₂ exposure metrics. Overall, the variation of AQ-DIs reflected that the physical characteristics of each individual ranged more widely than AQs. Spatial variations are seen in Supplementary Material Fig. S1. The average of the correlations of PM₁₀ between paired two monitoring stations was 0.94 ranging 0.78–1.00 and that of NO₂ was 0.84 ranging 0.33–0.97

Table 1

Subject characteristics and summary of symptoms and weather between August 2013 and December 2014.

Characteristics	Atopic dermatitis	Asthma
No. of subjects	177	70
Gender (male:female)	110:67	21:49
Age (years) ^a	2.0 ± 1.6	46.0 ± 11.3
Height (cm) ^a	83.9 ± 14.7	164.5 ± 6.9
Weight (kg) ^a	11.9 ± 4.0	63.4 ± 12.4
SCORAD ^{a,b}	31.1 ± 12.8	–
Total IgE (kU/L) ^a	366.4 ± 801.2	405.3 ± 578.5
Sensitization (%)		
Food allergens ^c	45.2	–
Inhalant allergens ^d	62.1	67.1
Presence of fever (%)	2.9	–
No. of smoking (%)	0	7 (10%)
No. of records (person-days)	29,683	13,989
Symptom presence (%)	44.8	14.4

^a All data are presented as mean ± standard deviation.

^b SCORAD, SCORing of Atopic dermatitis.

^c Sensitized by one of 5 common food allergens, including egg white, cow's milk, soybean, wheat, and peanut.

^d Sensitized by house dust mite (*Dermatophagoides pteronyssinus*, *D. farinae*) for atopic dermatitis, and one of 10 common inhalant allergens including *D. pteronyssinus*, *D. farinae*, tree pollen mixture, grass pollen mixture, weed pollen mixture, cockroach, cat, dog, *Alternaria alternata*, and *Aspergillus fumigatus* for asthma.

Table 2

Summary of exposure estimates for PM₁₀ and NO₂.

Pollutant	Exposure metric ^a	Atopic dermatitis		Asthma	
		Mean ± SD	IQR ^b	Mean ± SD	IQR
PM ₁₀	AQ1 (μg/m ³)	46.4 ± 26.7	30.9	48.7 ± 28.0	32.2
	AQ2 (μg/m ³)	35.3 ± 21.0	23.8	36.9 ± 21.7	24.5
	AQ1-DI (μg/kg-day)	39.6 ± 25.8	28.6	10.8 ± 6.4	7.3
	AQ2-DI (μg/kg-day)	30.2 ± 20.4	22.1	8.2 ± 4.9	5.6
NO ₂	AQ1 (ppb)	33.6 ± 13.8	18.9	35.0 ± 13.5	19.0
	AQ2 (ppb)	20.7 ± 17.6	25.0	23.7 ± 17.7	26.7
	AQ1-DI (μL/kg-day)	28.6 ± 14.4	18.1	7.8 ± 3.2	4.4
	AQ2-DI (μL/kg-day)	17.4 ± 15.7	20.5	5.3 ± 4.0	5.9

^a AQ1: daily average of ambient PM₁₀ and NO₂ measurements from the nearest air quality monitoring system (AQMS) station to residential houses; AQ2: measurements modified from AQ1 with indoor level and time activity for each individual; AQ1-DI: measurements modified from AQ1 with daily inhalation intakes of air pollutants; AQ2-DI: measurements modified from AQ2 with daily inhalation intakes of air pollutants. When paired *t*-tests were applied for exposure estimates, mean values of any pairs from four exposure metrics were different from each other with statistical significance (*P*-values < 0.0001).

^b Interquartile range.

Table 3
Spearman's rank correlation coefficient between exposure estimates for PM₁₀ and NO₂.

Pollutants	Exposure metrics ^a	AQ1	AQ2	AQ1-DI	AQ2-DI
PM ₁₀	AQ1	1.00	0.95	0.90	0.85
	AQ2		1.00	0.85	0.90
	AQ1-DI			1.00	0.95
	AQ2-DI				1.00
NO ₂	AQ1	1.00	0.64	0.84	0.63
	AQ2		1.00	0.50	0.96
	AQ1-DI			1.00	0.62
	AQ2-DI				1.00

P-values for all correlation coefficients are below 0.0001.

^a AQ1: daily average of ambient PM₁₀ and NO₂ measurements from the nearest air quality monitoring system (AQMS) station to residential houses; AQ2: measurements modified from AQ1 with indoor level and activity for each individual; AQ1-DI: measurements modified from AQ1 with daily inhalation intake of air pollutants; AQ2-DI: measurements modified from AQ2 with daily inhalation intake of air pollutants.

(P-values of the correlations were < 0.0001) which implied that NO₂ were more various in spatial distribution than PM₁₀.

Spearman's rank correlation coefficients of AQ2, AQ1-DI, and AQ2-DI for PM₁₀ in association with AQ1 were 0.95, 0.90, and 0.85, respectively, and those for NO₂ were 0.64, 0.84, and 0.63, respectively (Table 3). AQ2 and AQ2-DI for NO₂ were more differently distributed than for PM₁₀ reflecting that indoor NO₂ concentrations are more different from outdoors than PM₁₀.

3.3. Associations between air pollution estimates and allergic symptoms

The percent change in AD and asthma symptoms was analyzed by IQR according to increased concentrations of PM₁₀ or NO₂ (Table 4). For the analyses, 4 different exposure metrics were used after GLMM fitting of 29,683 and 13,989 person-day records from AD and asthma patients, respectively. Complete results across all lags are shown in Fig. 4.

The relationship between aggravated allergic symptoms and exposure to PM₁₀ was found to be statistically significant and consistent using the 4 metrics to estimate exposure. As shown in Table 4, with increases in PM₁₀ level by IQR, AD symptoms increased by 8.28% (95% CI: 3.23–13.58) and 7.02% (95% CI: 2.22–12.05) for exposures based on AQ1 (IQR: 30.92 µg/m³) and AQ2 (IQR: 23.75 µg/m³), respectively. With an increase in PM₁₀ by IQR, AD symptoms increased by 7.59% (95% CI: 2.35–13.10) and 4.34% (95% CI: −0.45–9.37) for AQ1-DI (IQR: 28.59 µg/kg-day) and AQ2-DI (IQR: 22.06 µg/kg-day), respectively. The

effects of NO₂, however, were not statistically significant except AQ2-DI for AD. A stronger relationship between PM₁₀ exposure and the presence of asthma symptoms was found compared to AD. With increased PM₁₀ by IQRs of AQ1 (IQR: 32.2 µg/m³), AQ2 (IQR: 24.5 µg/m³), AQ1-DI (IQR: 7.3 µg/kg-day), and AQ2-DI (IQR: 5.6 µg/kg-day), asthma symptoms increased by 9.42% (95% CI: 0.22–19.46), 11.05% (95% CI: 1.92–20.99), 12.28% (95% CI: 2.65–22.81), and 12.65% (95% CI: 3.24–22.93), respectively. Interestingly, the adverse effect of PM₁₀ were robust in female in both AD and asthma. As with AD, the effects of NO₂ on asthma symptoms were not statistically significant.

As shown in Fig. 4, PM₁₀ effects on AD and asthma had lagged effect at least up to 3 days. The lagged effect of PM₁₀ was clearer in AQ1 and AQ1-DI in both allergic diseases. In contrast, no lagged effect was shown in NO₂. When the moving average level of PM₁₀ during the previous 3 days and the current day (LAG0–3) increased by IQR based on AQ1 and AQ1-DI, AD symptoms increased by 19.01% (95% CI: 11.38–27.17) and 17.53% (95% CI: 9.70–25.92), respectively. Conversely, the effect sizes of AQ2 and AQ2-DI were 8.65% (95% CI: 3.49–14.07) and 7.22% (95% CI: 1.95–12.77), respectively, as shown in Fig. 4A. This pattern was also seen in the results for asthma symptoms, particularly in LAG0–3, although the differences were smaller than with AD (Fig. 4B).

Regarding uncertainty, variances for the effect of PM₁₀ on AD symptoms in children based on the four metrics were similar. Variances for NO₂, however, were higher in AQ2 and AQ2-DI, which considered indoor levels of NO₂ and time spent indoors (Fig. 4). This pattern was also shown in asthmatic adults. Among the four metrics, the estimated effect of NO₂ on the presence of allergic symptoms based on AQ2 had the largest variance.

4. Discussion

In the present study, four exposure metrics for PM₁₀ and NO₂ were applied at an individual level to compare their effects on allergic symptoms in patients with childhood AD and adult asthma. The results suggest that exposure to PM₁₀ is associated with aggravation of AD and asthma symptoms. The effect sizes and uncertainties of the health effect estimation were affected by the exposure metrics used in association analysis. This study assessed the health effect of PM₁₀ and NO₂ using exposure metrics that considered both time-weighted averages of ambient concentration and daily inhalation intakes at an individual level. To the best of our knowledge, this is the first study to evaluate the association between diverse exposure metrics of air pollution and allergic symptoms. Estimation of personal exposures in this study can be

Table 4
Percent change in symptoms of atopic dermatitis and asthma per increase in interquartile range in PM₁₀ and NO₂ concentrations on the day of exposure by different exposure metrics.

Disease	Air pollutant	Exposure metrics ^a	Total	Male	Female
Atopic dermatitis	PM ₁₀	AQ1	8.28 (3.23, 13.58)*	4.28 (−1.83, 10.77)	16.18 (7.35, 25.74)*
		AQ2	7.02 (2.22, 12.05)*	5.37 (−0.59, 11.68)	10.52 (2.47, 19.20)*
		AQ1-DI	7.59 (2.35, 13.10)*	3.83 (−2.58, 10.66)	14.72 (5.86, 24.33)*
		AQ2-DI	4.34 (−0.45, 9.37)	4.87 (−1.28, 11.39)	4.51 (−3.09, 12.70)
			−2.02 (−7.64, 3.93)	2.76 (−4.62, 10.70)	−9.85 (−18.29, −0.55)*
	NO ₂	AQ1	1.44 (−7.86, 11.68)	2.24 (−9.24, 15.17)	0.41 (−14.84, 18.40)
		AQ2	1.64 (−4.69, 8.38)	3.58 (−4.56, 12.41)	−1.19 (−10.97, 9.66)
		AQ1-DI	14.08 (5.08, 23.85)*	3.67 (−6.62, 15.09)	34.38 (17.76, 53.36)*
		AQ2-DI	9.42 (0.22, 19.46)*	−8.12 (−24.21, 11.39)	12.60 (1.96, 24.36)*
			11.05 (1.92, 20.99)*	−6.40 (−22.47, 13.00)	14.75 (4.15, 26.43)*
Asthma	PM ₁₀	AQ1	12.28 (2.65, 22.81)*	−5.19 (−20.55, 13.14)	15.32 (3.78, 28.14)*
		AQ2	12.65 (3.24, 22.93)*	−5.94 (−20.83, 11.75)	16.49 (5.09, 29.12)*
		AQ1-DI	8.02 (−2.83, 20.09)	26.71 (−0.49, 61.34)	6.89 (−5.08, 20.37)
		AQ2	6.86 (−9.91, 26.74)	33.45 (−9.69, 97.19)	4.77 (−13.5, 26.91)
		AQ1-DI	6.83 (−4.28, 19.22)	26.09 (−0.28, 59.44)	5.27 (−7.18, 19.40)
	NO ₂	AQ2-DI	9.34 (−7.24, 28.87)	44.29 (0.14, 107.90)*	5.84 (−12.4, 27.88)

^a AQ1: daily average of ambient PM₁₀ and NO₂ measurements from the nearest air quality monitoring system (AQMS) station to residential houses; AQ2: measurements modified from AQ1 with indoor level and activity for each individual; AQ1-DI: measurements modified from AQ1 with daily inhalation intake of air pollutants; AQ2-DI: measurements modified from AQ2 with daily inhalation intake of air pollutants. When paired t-tests were applied for exposure estimates, differences in effect sizes between exposure metrics were not statistically significant except for the difference between AQ1-DI and AQ2-DI for NO₂ in atopic dermatitis.

* P < 0.05.

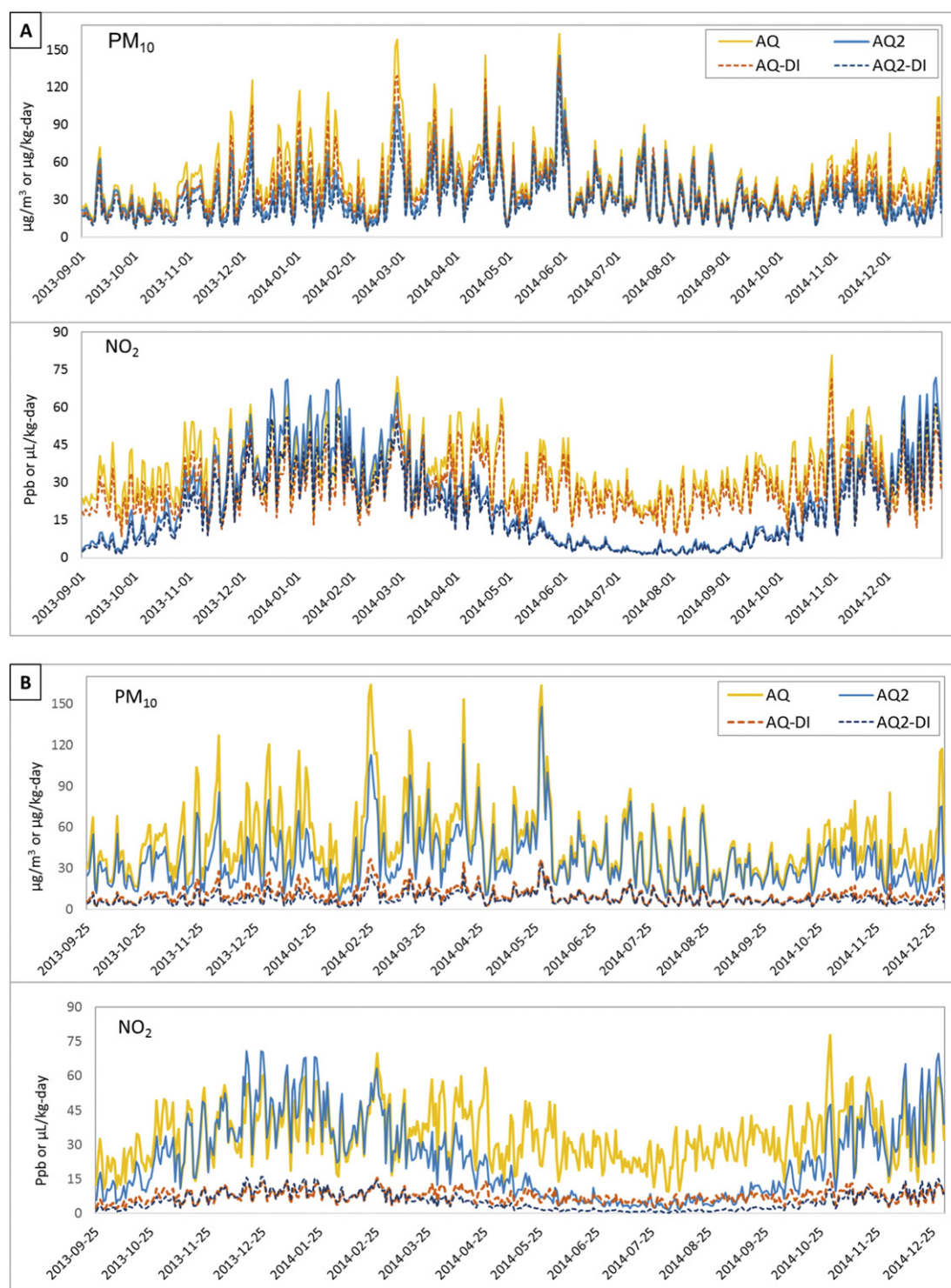


Fig. 3. Temporal variation of 4 exposure estimates of PM₁₀ and NO₂ in patients with atopic dermatitis (A) and asthma (B). AQ1, daily average of ambient PM₁₀ and NO₂ measurements from nearest air quality monitoring system (AQMS) station to residential houses; AQ2, measurements modified from AQ1 with indoor level and time activity for each individual; AQ1-DI, measurements modified from AQ1 with daily inhalation intake of air pollutants; AQ2-DI, measurements modified from AQ2 with daily inhalation intake of air pollutants.

applied to guide future research on estimating substantial personal exposures to air pollutants. This information could be used to improve epidemiological studies that consider microenvironments and inhalation capacity.

The four different exposure estimates for PM₁₀ and NO₂ in the present study showed significantly different means and variations, and thus differently affected associations between air pollution and allergic symptoms. The effect sizes of PM₁₀ exposure on asthma symptoms

were larger in AQ-DIs than in AQs in all lagged models, and they were more precise in some models, such as LAG0–3. These patterns were not found in AD, implying that asthma symptoms are more sensitive to the inhalation capacity of each individual than AD symptoms. These results suggest that exposure metrics considering individual characteristics such as inhalation capacity are potentially recommended for epidemiological studies on the association of air pollution and respiratory diseases. The impact of exposure to air pollutants via inhalation may

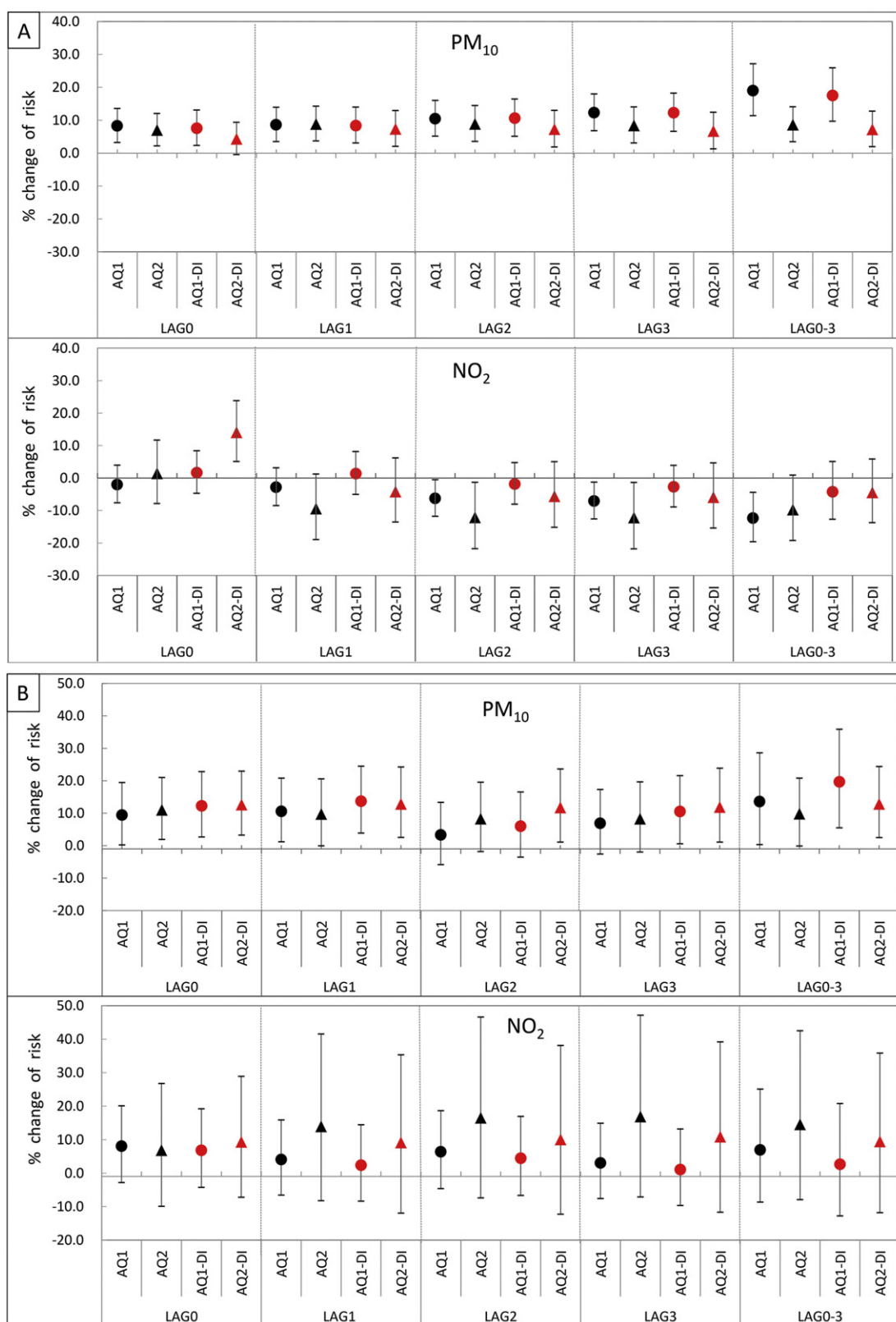


Fig. 4. Effects of PM₁₀ and NO₂ on atopic dermatitis (A) and asthma symptoms (B) according to exposure metrics and lag time. Effect size is expressed by percent change of clinical symptoms per change of interquartile range (IQR) in concentrations of PM₁₀ and NO₂. AQ1, daily average of ambient PM₁₀ and NO₂ measurements from the nearest air quality monitoring system (AQMS) station to residential houses; AQ2, measurements modified from AQ1 with indoor level and time activity for each individual; AQ1-DI, measurements modified from AQ1 with daily inhalation intakes of air pollutants; AQ2-DI, measurements modified from AQ2 with daily inhalation intakes of air pollutants; LAG0, effect of exposure to air pollutants on allergic symptoms on the same day; LAG1, LAG2, and LAG3, lagged by 1, 2, and 3 days, respectively; LAG0–3, effect of moving average for 4 days from the previous 3 days through the current day.

be minimal in AD patients. However, it does not imply that it is not necessary to improve exposure assessment in the studies of AD. Further studies are required to evaluate the exposure metrics with indoor concentrations and inhalation capacities.

The effects of moving average level of PM₁₀ (LAG0–3) on AD symptoms were greater in AQ1 (19.01% [95% CI: 11.38–27.17]) and AQ1-DI (17.53% [95% CI: 9.70–25.92]) than AQ2 (8.65% [95% CI: 3.49–14.07]) and AQ2-DI (7.22% [95% CI: 1.95–12.77]). Considering that AQ2 and AQ2-DI reflect indoor concentration and time to spend indoors, these results imply that epidemiological study on AD only based on ambient PM₁₀ level may overestimate the effect of PM₁₀ on AD symptoms.

In all lagged models, exposure to PM₁₀ showed a clear relationship with allergic symptoms. That is, with higher levels of PM₁₀ exposure, allergic symptoms presented more frequently. By contrast, the effect of NO₂ exposure showed no consistent relationship. This difference between PM₁₀ and NO₂ might be explained by the fact that indoor levels of NO₂ were used to calculate AQ2 with relatively higher uncertainty compared to PM₁₀. The R² value of the model for the I/O ratio of NO₂ was 0.29, which could increase the uncertainty of the indoor concentration estimation. The R² value for the NO₂ I/O ratio was not high because indoor activity such as cooking was not included in the estimation model. When the time spent cooking was included in the I/O ratio model for NO₂ in our previous study (Lee et al., 2016a), R² increased to 0.54. In this study, ambient temperature was only used in the regression model for I/O ratio without using other variables, such as time spent cooking, and the I/O ratio was extrapolated. The lower R² of NO₂ I/O ratio model based on a small sample size implies that the estimated indoor concentrations of NO₂ might increase uncertainties in the assessment of NO₂ effect on allergic diseases. Another reason why the effect of NO₂ was not significant or even showed negative relationships with AD symptoms might be due to two-pollutant models. As suggested by Tolbert et al. (2007), multi-pollutant models including PM₁₀ and NO₂ in the same model consider the possibility of complex interactions among pollutants. Because positive relationships of allergic symptoms with PM₁₀ were more determinant than those with NO₂, the NO₂ effect on allergic symptoms might be reduced by adjusting PM₁₀. When single-pollutant models were applied with adjustment for the same confounding factors as two-pollutant models, the effects of NO₂ on asthma symptoms were significantly positive in all lagged models. The effects on AD symptoms were also positive in unlagged models, although they were not statistically significant (Supplementary material, Fig. S2).

Our study has several limitations. Firstly, we estimated daily intakes for PM₁₀ and NO₂ using inhalation intake alone. Other exposure routes, such as dermal and dietary routes, were not considered. This was due to lack of data available for exposure factors (e.g., there are no studies on the uptake factor of PM₁₀ through dermal absorption). Moreover, the health effects of PM₁₀ and NO₂ are exacerbations of airway diseases resulting in decreased lung function (Lin et al., 2002; Pope, 2000; Schwartz, 1993). The ADI used in this study can represent daily intake for health effect studies on the basis of the fact that the health effects of exposure to particulate matter through inhalation are associated with pulmonary function and respiratory disease (Pope, 2000). However, because inhalation rates that we used were assessed by pre-existing exposure factors instead of measuring in each individual, they did not reflect weather-driven differences in actual activity. Secondly, time spent in the office or other locations away from residences was not considered, particularly in asthmatic adults. This was due to a lack of information on office addresses and indoor concentrations of PM₁₀ and NO₂. Further studies are needed to improve the estimation method at an individual level considering indoor and outdoor concentrations of air pollutants in locations away from residences. Finally, when we investigated the autocorrelations of symptoms for each individual using autocorrelation function, autocorrelation with several days was detected in both asthma and AD symptoms. That we did not control the autocorrelations for each individual is also one of limitations of our study. Further studies

are required to improve the model we used considering both random effect for each subject and autocorrelation of symptoms of each subject at the same time.

5. Conclusions

Exposure estimates of PM₁₀ and NO₂ varied by exposure metrics, and the associations of PM₁₀ with aggravated symptoms of AD in children and asthma in adults were robust. Additionally, the effect sizes of exposure to air pollutants varied by exposure estimation method. Our results suggest that exposure metrics considering individual behaviors and physical status such as inhalation capacity may provide better estimation for studies on the effect of air pollution on asthma.

Ethical considerations

We obtained ethical approval from the Institutional Review Board at Samsung Medical Center (IRB No: 2013-05-009).

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COI declaration

The authors have no competing financial interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.scitotenv.2016.11.090>.

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