

**ORIGINAL ARTICLE**

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## **Clinical and Immunological Effects of a Forest Trip in Children with Asthma and Atopic Dermatitis**

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### **ABSTRACT**

Asthma and atopic dermatitis are common allergic diseases, and their prevalence has increased in urban children. Recently, it is becoming understood that forest environment has favorable health effects in patients with chronic diseases. To investigate favorable clinical and immunologic effects of forest, we examined changes in clinical symptoms, indirect airway inflammatory marker, and serum chemokines before and after a short-term forest trip.

The forest trips were performed with 21 children with asthma and 27 children with atopic dermatitis. All participating children were living in air polluted urban inner-city. We measured spirometry and fractional exhaled nitric oxide (FeNO) in children with asthma and measured scoring atopic dermatitis (SCORAD) index and Thymus and Activation-Regulated Chemokine (TARC)/CCL17 and Macrophage-Derived Chemokine (MDC)/CCL22 levels in children with atopic dermatitis before and after the forest trip. Indoor air pollutants such as indoor mold, particulate matter 10 (PM<sub>10</sub>) and total volatile organic compounds (TVOCs) of each child's home and the accommodations within forest were measured.

A significant increase in forced vital capacity (FVC) and a significant decrease in FeNO were observed after the forest trip in children with asthma. SCORAD indices and MDC/CCL22 levels were significantly decreased after the forest trip in children with atopic dermatitis. Airborne mold and PM<sub>10</sub> levels in indoor were significantly lower in the forest accommodations than those of children's homes; however, TVOC levels were not different between the two measured sites.

Short-term exposure to forest environment may have clinical and immunological effects in children with allergic diseases who were living in the urban community.

**Keywords:** Asthma; Atopic dermatitis; CCL22; Forest; Nitric oxide; Particulate matter; CCL17; Urban

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# Effects of a Forest Trip in Children with Asthma and Atopic Dermatitis

## INTRODUCTION

The prevalence of chronic allergic diseases, such as asthma and atopic dermatitis, in developed countries has been increasing in recent decades and has been particularly noted in urban areas.<sup>1,2</sup> The economic burden of these diseases increases, and there is also concern about known side effects after long-term use of corticosteroids. It is necessary to establish effective counter-measures using less-expensive and safe methods while considering long term treatments that have established efficacy for relieving burden of chronic allergic diseases.

Forest environment has been known to exert beneficial effects on human health. The aroma of plants and other various factors in forest environment including clean fresh air and mild climate would be likely to offer these favorable benefits.<sup>3</sup> For these reasons, forest environment has favorable effects on human physiologic and psychological functions in patients with chronic diseases, such as allergies or respiratory diseases.<sup>4</sup> Also, a few studies reported that natural killer (NK) cells are involved in immunologic mechanisms of forest environment through anti-inflammatory properties and promoting immune function.<sup>5-7</sup>

Nonetheless exposure to forest through walking, recreation, and forest bathing has been linked to positive effects on health, most previous studies have focused on limited clinical effects.<sup>4</sup> We thus hypothesized that a short-term exposure to forest environment would have not only clinical improvement but also immunologic effects on chronic allergic diseases.

Exhaled nitric oxide (eNO) is a non-invasive marker of airway inflammation. In recent years, fractional eNO (FeNO) has become a valuable tool for diagnosis and monitoring of children with asthma.<sup>8,9</sup> Thymus and activation-regulated chemokine (TARC/CCL17) are ligands for CC chemokine receptor 4 (CCR4) that is selectively expressed on Th2 cells and may play an important role in the pathogenesis of allergic diseases.<sup>10,11</sup> The serum levels of macrophage-derived chemokine (MDC/CCL22) which are also a selective chemoattractant for CCR4 were increased and related to disease activity in patients with atopic dermatitis.<sup>12,13</sup> Thus, we investigated clinical and immunological effects of forest environment in children with allergic diseases by measuring changes in

disease severity and immunologic markers, such as FeNO, TARC/CCL17, and MDC/CCL22 before and after the forest trip.

## MATERIALS AND METHODS

### Study Population and Design

A total of 48 children aged 7–12 years who had asthma or atopic dermatitis were recruited from the Allergy Clinic of Korea University Anam Hospital and a local public health center located in a polluted urban area. Forest activities were performed at the Saneum National Recreation Forest during August 1~4, 2012 for children with asthma and during August 8 ~11, 2012 for children with atopic dermatitis. This national forest is located in the northeast part of the Korean peninsula and is approximately 80 km away from the Seoul metropolitan city (Figure 1). The forest covers an area of 2,140 ha and comprises mostly Fir trees. This study was approved by the institutional review board of Korea University Anam Hospital (AN12098-001). Parents gave written informed consents for their children to participate in the study.

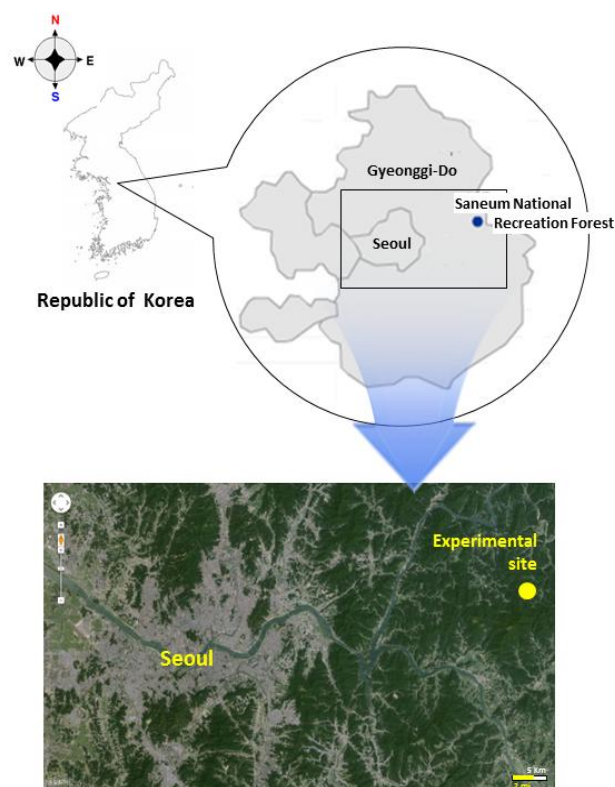


Figure 1. Location of the experimental site

### Forest Trip Program

The forest trip program mainly consisted of forest outdoor and educational activities, lasting for 4 days and 3 nights. In the forenoon of each day, all children were asked to walk around the predetermined course for approximately 1 hour and participate in recreational activities for 1 hour in the forest. In the afternoon, recreational games and activities were mostly performed outdoors. The outdoor recreation activities included mini Olympics, treasure hunt, and swimming. In the evening, lectures on allergic diseases and self-initiative learning through games were held indoors. Major indoor recreation activities consisted of origami, making potential allergens with toy clay, and puzzles on environmental risk factors of allergic diseases (Figure 2).

### Pulmonary Function Tests

Forced expiratory volume in 1 second (FEV<sub>1</sub>) and forced vital capacity (FVC) were measured using a microspirometer (Microspiro-106 HI 298, Chest, Tokyo, Japan), in accordance with the recommendations of the American Thoracic Society<sup>14</sup> before and after the forest trip for children with asthma. FEV<sub>1</sub> and FVC were measured three times for each child and the highest value among the three values was recorded. The values were compared with the reference standard based on predicted values for Korean children.

### Measurement of FeNO

Exhaled NO was measured for children with asthma 2 weeks before, immediately before and after the forest trip according to ATS/ERS recommendations<sup>15</sup> using a chemiluminescence analyzer (NIOX MINO analyzer, Aerocrine, Sweden). We followed the manufacturer's recommendations: inhalation of NO free air to total lung capacity, immediately followed by full exhalation against a positive mouthpiece counter pressure at a flow rate of 50 mL/s into an on-line chemiluminescence analyzer to avoid any nasal contamination.

### SCORAD Index

A diagnosis of atopic dermatitis was performed on the basis of clinical history of recurrent itching, and morphologies and distributions of skin lesions. The severity of atopic dermatitis was evaluated using the scoring of atopic dermatitis (SCORAD) index<sup>16</sup> by the

same pediatrician at 2 weeks before, immediately before and after the forest trip.

### Measurement of Total IgE Levels and Eosinophil Counts

Venous blood samples from each child were collected immediately before the forest trip. Serum total IgE levels were measured using a Coat-A-Count Total IgE IRMA (Diagnostic Products Co, Los Angeles, CA, USA) according to the manufacturer's instructions. The number of peripheral blood eosinophils was counted with blood samples containing EDTA8 using an automated hematology 129 analyzer (Coulter Counter STKS, Beckman Coulter, Fullerton, CA, USA).

### Measurement of Serum TARC/CCL17 and MDC/CCL22 Levels

The serum levels of TARC/CCL17 and MDC/CCL22 were measured in children with atopic dermatitis before and after the forest trip using a sandwich enzyme-linked immunosorbent assay (Tecan Group Ltd., Männedorf, Switzerland) according to the manufacturer's recommendations. Detection limits of TARC/CCL17 and MDC/CCL22 were 7 pg/mL and 62.5 pg/mL, respectively.

### Measurements for the Level of Indoor Pollutants

Air sampling of airborne mold, particulate matter 10 (PM<sub>10</sub>), and volatile organic compounds (VOCs) was conducted over 8 hours in the children's homes and the forest accommodations. For collecting airborne mold, we used the one-stage Andersen sampler (Andersen Instruments Inc., Atlanta, GA, USA) with a Gast pump (Model No. 1531-107B G289X; Gast Manufacturing, Inc., Benton Harbor, MI, USA) at a flow rate of 28.98 L/min for 10 minutes. Colony numbers were counted on the plates to determine airborne mold concentrations after a 4-day incubation period at approximately 20°C–25°C. PM<sub>10</sub> concentrations were measured by an optical particle counter (OPC; Model 1.108; Grimm Technologies, Inc., Douglasville, GA, USA). TVOC samples were collected by thermal desorption tubes (Tenax TA; Supelco, USA) with a minipump (MP-Σ30; Sibata, Japan) at a flow rate of 0.1 L/min for 30 minutes and were analyzed using a thermal disorder (Ultra TD & Unity; Markes, UK) interfaced with a gas chromatograph (Agilent 6890; Agilent Technologies,

## Effects of a Forest Trip in Children with Asthma and Atopic Dermatitis

USA) or a mass selective detector (Agilent 5975B, Agilent Technologies, USA).

### Statistical Analysis

Data are presented as mean  $\pm$  standard deviation (SD). The values of serum total IgE, blood eosinophils, FeNO, TARC/CCL17, MDC/CCL22 and indoor pollutant concentrations were log transformed before statistical analysis and presented as geometric means and their ranges of 1 SD. Paired *t*-tests were used to compare pulmonary function parameters and

chemokine concentrations before and after the forest trip. Repeated measure of ANOVA was applied to compare FeNO levels and SCORAD indices to compare the levels of 2 weeks before, immediately before and after the forest trip. Student *t*-tests were used to compare indoor pollutant levels between children's homes and the forest accommodations. All statistical analyses were performed using the SPSS software (version 17; SPSS Inc, Chicago, IL, USA). A *P* value of  $<0.05$  was considered statistically significant.



**Figure 2. The 4-day and 3-night forest trip program**

**Table 1. Clinical characteristics of study population**

Parameters	Children with asthma (n=21)	Children with atopic dermatitis (n=27)
Age (yr), mean $\pm$ SD	10.2 $\pm$ 1.6	9.7 $\pm$ 1.3
Boy (%)	14 (66.7)	8 (29.6)
Total IgE (IU/mL)*	275.4 (117.5-645.7)	371.5 (97.7-1412.5)
Blood eosinophils (/ $\mu$ L)*	257.6 (123.3-538.3)	349.9 (538.3-1030.4)

\*Geometric mean (range of 1 SD)

## RESULTS

### Study Population

The clinical characteristics of the 48 children participating in this study are shown in Table 1. There were 21 children with asthma and 27 children with atopic dermatitis. The geometric means (range of 1 SD) of serum total IgE were 275.4 IU/mL (117.5-645.7) in children with asthma and 371.5 IU/mL (97.7-1412.5) in children with atopic dermatitis. Blood eosinophils were 257.6 / $\mu$ L (123.3 – 538.3) in children with asthma and 349.9 / $\mu$ L (538.3-1030.4) in children with atopic dermatitis.

### Clinical Outcomes

Pulmonary function parameters of children with asthma and serum chemokine concentrations of children with atopic dermatitis before and after the forest trip are presented in Table 2. The mean FVC was significantly increased after the forest trip (95.8  $\pm$  13.3) than before the forest trip (92.0  $\pm$  11.3) ( $P=0.018$ ), but such a significant difference was not observed in FEV<sub>1</sub> (92.9  $\pm$  11.0 vs. 91.2  $\pm$  9.9) ( $p=0.224$ ). The geometric mean (range of 1SD) serum TARC/CCL17 after the forest trip (108.9 pg/mL [37.2-319.2]) was not significantly different from that before the forest trip

(132.1 pg/mL [47.8-365.6]) ( $p=0.217$ ). However, serum MDC/CCL22 levels after the forest trip (668.3 pg/mL [494.3–903.6]) were significantly decreased than that before the forest trip (760.3 pg/mL [538.3-1030.4]) ( $p=0.007$ ).

The geometric mean (range of 1 SD) of FeNO at immediately before the forest trip (23.7 ppb [14.2-39.5]) was not significantly changed from that of 2 weeks before the forest trip (24.3 ppb [14.8-40.0]); however, it was significantly decreased after the forest trip (16.4 ppb [9.1-29.4]) ( $p=0.001$ ) (Figure 3).

The mean ( $\pm$  SD) SCORAD index after the forest trip (12.3  $\pm$  7.8) was significantly different from those of 2 weeks before the forest trip (21.1  $\pm$  8.3) and immediately before the forest trip (20.2  $\pm$  8.1) ( $p=0.001$ ) (Figure 4).

### Indoor Pollutant Levels

Figure 5 shows the 8-hr average concentrations of airborne pollutants in indoor. Mean  $\pm$  SD (log 10) airborne mold concentrations of the accommodations within forest (2.14  $\pm$  0.12 CFU/m<sup>3</sup>) was significantly lower than either those of homes of children with asthma (2.70  $\pm$  0.19 CFU/m<sup>3</sup>) ( $p=0.001$ ) or those of homes of children with atopic dermatitis (2.58  $\pm$  0.13 CFU/m<sup>3</sup>) ( $p=0.003$ ). Similarly, PM<sub>10</sub> levels of the

**Table 2. Pulmonary function parameters, TARC/CCL17 and MDC/CCL22 in children with asthma or atopic dermatitis**

Parameters	Before the forest trip	After the forest trip	P. values
Children with asthma (n = 21)			
FEV <sub>1</sub> (% predicted)	91.2 $\pm$ 9.9	92.9 $\pm$ 11.0	0.224
FVC (% predicted)	92.0 $\pm$ 11.3	95.8 $\pm$ 13.3	0.018
Children with atopic dermatitis (n=27)			
TARC/CCL17 (pg/mL)*	132.1 (47.8-365.6)	108.9 (37.2-319.2)	0.217
MDC/CCL22 (pg/mL)*	760.3 (538.3-1030.4)	668.3 (494.3-903.6)	0.007

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1sec; FVC, forced vital capacity; TARC, thymus and activation-regulated chemokine; MDC, macrophage-derived chemokine.

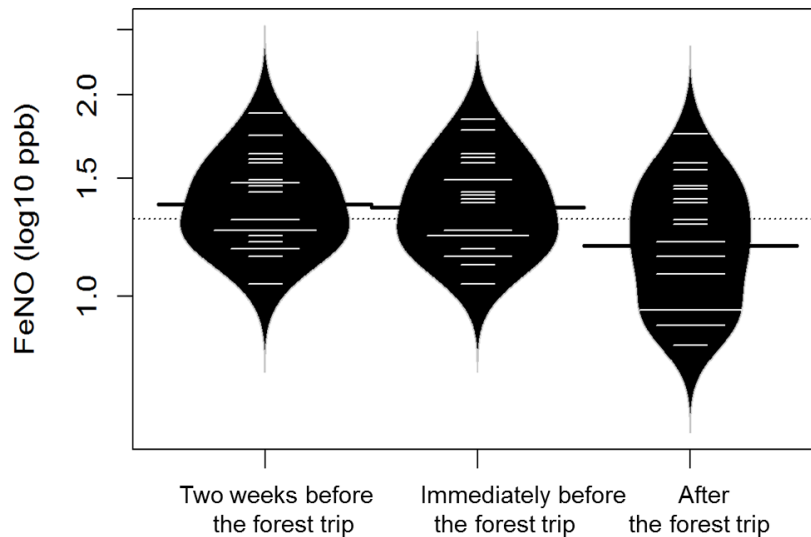
Data are presented as mean  $\pm$  SD.

\*Geometric mean (range of 1 SD).

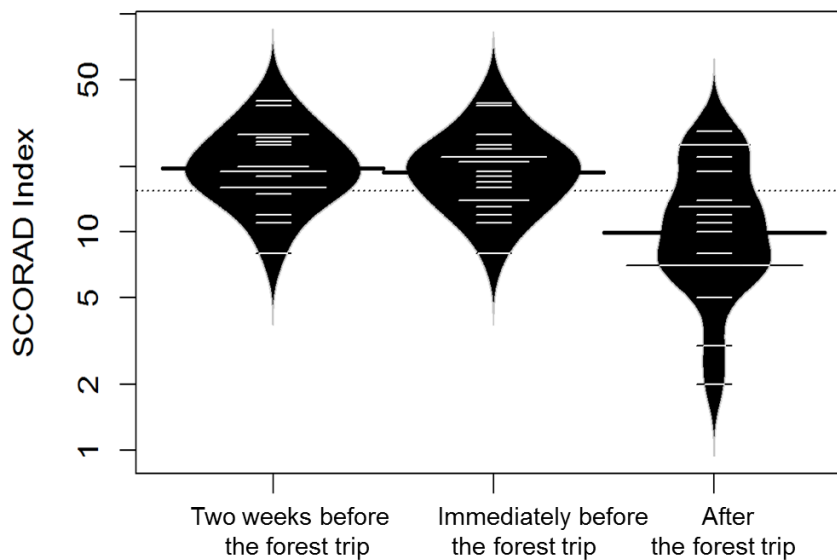
## Effects of a Forest Trip in Children with Asthma and Atopic Dermatitis

accommodations within forest ( $1.12 \pm 0.27 \mu\text{g}/\text{m}^3$ ) were significantly lower than those homes of children with asthma ( $1.72 \pm 0.10 \mu\text{g}/\text{m}^3$ ) ( $p=0.001$ ) and those of homes of children with atopic dermatitis ( $1.60 \pm 0.78$

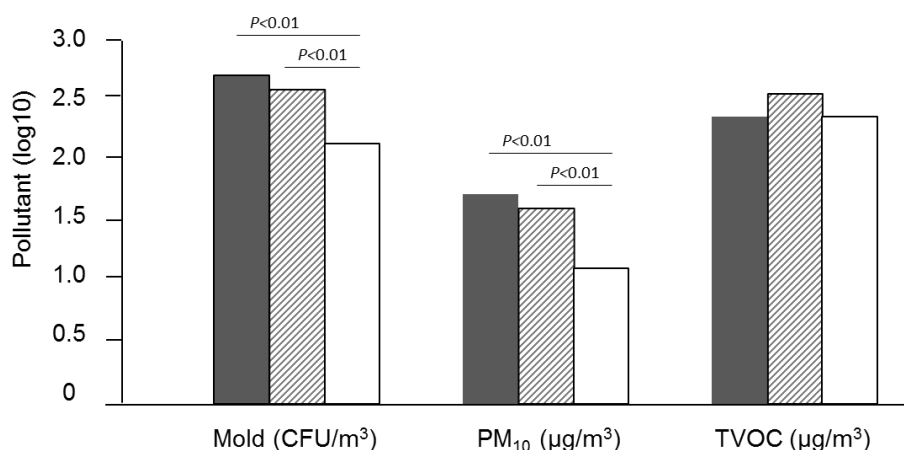
$\mu\text{g}/\text{m}^3$ ) ( $p=0.001$ ), respectively. No significant differences of the TVOCs concentrations were observed between children's homes and the accommodations within forest.



**Figure 3. Distributions of FeNO levels measured 2 weeks before, immediately before, and after the forest trip in children with asthma**



**Figure 4. Distributions of SCORAD indices measured 2 weeks before, immediately before, and after the forest trip in children with atopic dermatitis**



**Figure 5.** The levels of airborne mold and pollutants in indoor within homes of children with asthma (■), homes of children with atopic dermatitis (▨) and the accommodations in forest (□)

## DISCUSSION

We demonstrated significant clinical and immunologic effects after the forest trip in children with asthma or atopic dermatitis in the present study. Pulmonary function parameters were significantly increased, and FeNO was significantly decreased after the forest trip in children with asthma. Similar clinical and immunologic improvements were also observed in children with atopic dermatitis.

We observed a significant improvement in FVC after the forest trip in children with asthma. Less exposure to allergen, in particular attributed to air pollution,<sup>17</sup> as well as exposure to forest environment and regular exercise may contribute to improved lung functions in children with asthma. However, there was no significant increase in FEV<sub>1</sub> after the forest trip. Most of our children had mild-to moderate well-controlled asthma and their baseline lung functions were near normal. Thus, it may be little room for improvement in airway obstruction (FEV<sub>1</sub>).

In recent years, FeNO has become a valuable tool to assess diagnosis and to monitor of asthma in childhood.<sup>8,9</sup> In many studies, FeNO measurements have well correlated with symptoms and disease severity in children with asthma. FeNO assessment is simple to perform and easy to measure; thus, it was acceptable for the pediatric population particularly at the place other than clinics. In the present study, the FeNO levels of children with asthma were significantly

decreased after the forest trip than those of 2 weeks before and immediately before the forest trip. Exposure to environmental pollutants as well as allergens in urban environment can enhance allergic airway inflammations in children with asthma.<sup>17-19</sup> Thus, an increase in FeNO levels reflects increased airway inflammation and is related to worsening of symptoms in patients with asthma. The significant decrease in FeNO after the forest trip in our study may be thought to be a positive effect of forest exposure.

Children living in the urban environment were exposed to elevated indoor allergens and indoor air pollutants. Indoor pollutants have been shown to promote development of airway allergy by adjuvant effects.<sup>18,19</sup> Furthermore, a previous study demonstrated that FeNO concentrations correlated with exposure to air pollutants, such as black carbon in children living in the urban community.<sup>20</sup> In the present study, the levels of airborne pollutants in indoor within the children's homes were lower than those of the forest accommodations.

Little is known about immunologic mechanisms involved in forest activities until now. A few previous studies reported enhanced immune functions, as evidenced by increases in NK cell activity in patients who visit a forest environment.<sup>5,6</sup> Exposure to beneficial chemicals (*i.e.*, phytoncides) released from a forest is often cited as a scientific basis for the positive effects of forest environment on human health. Moreover, the levels of airborne mold and PM<sub>10</sub> in the

## Effects of a Forest Trip in Children with Asthma and Atopic Dermatitis

accommodations within forest were lower than those of children's homes. Thus, avoidance of risk factors could contribute to improvement in allergic symptoms.<sup>17</sup> These results indicate that air pollutants under environmental control in indoor may help patients with allergic diseases alleviate their symptoms.

TARC/CCL17 and MDC/CCL22 are Th2 chemokines and have been used to explain the involved immunological mechanisms of allergic diseases, which are highly expressed in the skin of patients with atopic dermatitis.<sup>10,11</sup> In our study, significant decreases in MDC/CCL22 levels as well as in SCORAD indices in children with atopic dermatitis were observed after the forest trip. These findings are consistent with those of previous studies demonstrating that the association between decreases in MDC/CCL22 levels and improvement in clinical severity of atopic dermatitis.<sup>21</sup> In particular, forest environment may exert a suppressive effect on immunological mechanisms contributing to severity of atopic dermatitis. This may be considered one of positive effects since it may reduce the use of corticosteroids. Although the decreases in the MDC/CCL22 levels support a positive immunological effect of outdoor activities in forest on atopic dermatitis, further studies are necessary to elucidate the precise role of MDC/CCL22 in the pathophysiology of atopic dermatitis.

It still remains to be solved how long doses activities in the forest effect on improvement of symptoms for allergic diseases or what kind of causal mechanisms in the forest environment have occurred. We did not observe these long-term effects after the trip as well, although previous studies reported that forest effects last for 7 days or more than 30 days after trips.<sup>5,6</sup> Moreover, we were unable to compare exposure levels to allergens between the children's homes and the forest accommodations. Therefore, we could not exclude the effect of avoidance of allergens on clinical and immunological improvements of our subjects. Lastly, we did not compare same effects on healthy children in this study.

In summary, we found significant clinical and immunological improvements in children with asthma or atopic dermatitis after exposure to forest environment for several days. In particular, we observed increases in lung functions and decreases in FeNO levels in children with asthma and decreases in SCORAD indices and serum immunologic parameters such as MDC/CCL22, in children with atopic

dermatitis. Either control of polluted urban or environment fresh and clean air in a forest, or both, may contribute to these findings. Our findings support that forest trip may have beneficial effects on human immune function and provide an complementary treatment modality, especially in children with chronic allergic diseases who live in an urban inner-city community.

### ACKNOWLEDGEMENTS

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