Allergy Asthma Immunol Res. 2021 May;13(3):468-478
https://doi.org/10.4168/aair.2021.13.3.468
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

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Harmful Effect of Indoor Formaldehyde on Atopic Dermatitis in Children: A Longitudinal Study

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OPEN ACCESS

Received: Jun 11, 2020
Revised: Sep 7, 2020
Accepted: Oct 5, 2020

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Disclosure
There are no financial or other issues that might lead to conflict of interest.

ABSTRACT

Purpose: Evidence supporting a link between indoor formaldehyde exposure and atopic dermatitis (AD) in humans is limited. The purpose of this longitudinal study was to investigate whether AD symptoms in children could be affected by indoor formaldehyde levels in ordinary households.
Methods: Fifty-five children with moderate-to-severe AD aged under 18 years were enrolled as a panel. They were followed up from February 2019 through February 2020. Indoor formaldehyde levels of patients' houses and their AD symptoms were repeatedly measured on a daily basis. The generalized linear mixed model was utilized for statistical analysis. Subdivision analysis was performed by stratifying patients by sex, body mass index, presence of parental allergy, and indoor environments including mold/dampness, temperature, and relative humidity (RH).
Results: A total of 4,789 person-days of AD symptom data were collected. The average concentration of formaldehyde was 13.6 ± 16.4 ppb, with the highest value found in spring (18.1 ± 20.6 ppb). Higher levels of formaldehyde were observed when there was parental smoking, increased indoor temperature over 25.5°C, or RH over 60% ($P < 0.0001$). When the effect size was compared between each season after controlling for ambient particulate matter, temperature, and RH, an increase in 10 ppb of formaldehyde increased AD symptoms by 79.2% (95% confidence interval [CI], 19.6–168.4) in spring and by 39.9% (95% CI, 14.3–71.2) in summer. AD symptoms in children aged 6–18 years appeared to increase significantly, whereas there was no significant increase in children under 6 years. When indoor temperature was over 25.5°C, an increase in formaldehyde by 10 ppb increased AD symptoms by 17.8% (95% CI, 3.9–33.6).
Conclusions: Indoor formaldehyde can exacerbate AD symptom in children with moderate-to-severe AD, particularly in spring and summer, even at allowable levels. Thus, minimizing exposure to indoor formaldehyde may be needed for the proper management of AD in children.

Keywords: Formaldehyde; atopic dermatitis; child; seasons; air pollution; fungi; smoke

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INTRODUCTION

The importance of indoor air quality is increasingly emphasized because people spend much time indoors. Pollutants commonly found in indoor air may have many harmful effects on health. One of the indoor air pollutants is formaldehyde, a chemical widely used in manufacturing processes. Formaldehyde is also a component of many end-use products, including building materials and consumer products such as antiseptics, cleaning agents, carpets, permanent press fabrics, cosmetics, preserved foods, paints, and furniture.[1] Formaldehyde is a highly reactive molecule that can directly irritate tissues upon contact. It is also known as an environmental pollutant that can cause sick building syndrome (SBS).[2,3] Epidemiological studies have suggested that formaldehyde can induce or aggravate allergic diseases such as asthma[4-7] and contact dermatitis.[8-11]

Atopic dermatitis (AD) is a chronic inflammatory skin disease mostly occurring in early childhood and predisposes to food allergy and atopic march.[12] The estimated prevalence of AD in Korean children aged 18 years or younger in 2014 was 5.8% according to an analysis of data from the Korean National Health Insurance Service.[13] The management of ongoing AD is a critical issue in public health. One basic principle in the management of AD is to avoid aggravating factors such as microbes, allergens, emotional stresses, meteorological factors, and pollutants.[14-16] Among many environmental triggers, formaldehyde is likely to induce skin barrier dysfunction in AD. In a single-blind study, formaldehyde exposure for 4 hours significantly increased transepidermal water loss (TEWL) in adult patients with atopic eczema, but not in control subjects.[17] In our previous study using a provocation test on the skin of the forearms, statistically significant increases in TEWL and skin pH 2 hours after exposure to airborne formaldehyde were found in normal healthy children, with more dramatic increases in children with AD.[18] These human studies demonstrated that short-term exposure to indoor airborne formaldehyde may directly impair the epidermal barrier and possibly raise concerns about worsening AD. However, data are unavailable to investigate whether AD symptoms, not skin barrier function, are influenced by continuous or repeated exposure to indoor formaldehyde at the level that patients encounter in real life. Thus, the objective of this longitudinal study was to examine the association between exposure to indoor formaldehyde and AD symptoms in children by measuring real-time formaldehyde concentrations in their houses and monitoring daily symptom scores.

MATERIALS AND METHODS

Study participants and clinical data

A total of 55 children (36 boys, 17 girls) aged under 18 years with AD living in Seoul Metropolitan Areas of Korea were enrolled as a panel. They were followed up from February 2019 to February 2020. The diagnosis of AD was made according to the Hanifin and Rajka criteria.[19] AD severity was assessed using the SCORing Atopic Dermatitis (SCORAD) index.[20] Only AD patients with the SCORAD score over 15 were enrolled, because patients with mild AD may not be sensitive to a small change in the indoor formaldehyde level. Total immunoglobulin E (IgE) and specific IgE against common food and inhalant allergens in peripheral blood were measured using ImmunoCAP (Thermo Fisher Scientific, Waltham, MA, USA). Sensitization was defined when the level of specific IgE was over 0.35 kU/L. Common allergens included egg white, cow's milk, soybean, wheat, peanut, *Dermatophagoides pteronyssinus*, and *D. farinae*.

https://doi.org/10.4168/aair.2021.13.3.468

Parents or children were instructed to record AD symptoms on a daily basis using a symptom diary designed to write the extent of subjective symptoms (itching and sleep disturbance) and the degree of objective signs (erythema, dryness, oozing, and edema) on a scale of 0 to 4.[21] The presence of AD symptoms was defined when each subjective symptom score was 2 or greater accompanied by at least 2 objective signs. This definition is based on the fact that our patients are not symptom-free even at baseline. All patients were instructed to take a daily bath or shower and apply moisturizers frequently during the study period. The intermittent use of low-potency topical corticosteroid (TCS) was allowed when needed. Along with symptom scores, they recorded the use of TCS and the presence of fever every day. Those who were allergic to inhalants or foods avoided exposure to the offending allergens.

When participants were enrolled, we also surveyed the presence of parental allergic diseases (asthma, AD, and allergic rhinitis), passive smoking status, the presence of mold or dampness as a household environment, and demographic information.

Written informed consent was obtained from the parent or guardian of each participating child. Study protocols were reviewed and approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2018-10-121).

Exposure assessment of indoor formaldehyde, temperature, and relative humidity (RH)

To assess indoor concentrations of formaldehyde, Breeze® (SENKO, Osan, Korea), a real-time sensor device, was used. Breeze® has a formaldehyde sensor, SSGSM-HCHO, to measure the level of formaldehyde based on electrochemical reactions. Assessment of the sensor was made by comparing it with an Interscan 4000 analyzer (Raeco-LIC, Bensenville, USA). Details are shown in **Supplementary Fig. S1**. Breeze® also has temperature and RH sensors. Breeze® was placed in the living room of each participant's house. Formaldehyde concentration, indoor temperature, and indoor RH were measured automatically every 10 minutes. Data were sent to and saved in the cloud. Upper and lower 10% of 10-minute interval data of each day were deleted and the average value of 24-hour data was calculated.

Covariates

Ambient environments, such as particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), temperature, and RH, are known to be associated with aggravation of AD symptoms in children.[15,22] Therefore, we obtained hourly $PM_{2.5}$ concentrations from the nearest air quality monitoring system (AQMS) station based on the home address of each participant. The average distance between the AQMS stations and patient residences was 1.90 ± 1.13 km. We matched daily AD symptom data of each patient with 24-hour average level of ambient $PM_{2.5}$. Daily outdoor temperature and RH were obtained from the Korean Meteorological Administration (KMA) and included in health effect models as confounding factors.

Statistical analysis

Considering that repeated measurement of allergic symptoms could provide longitudinal data with a binomial distribution, the generalized linear mixed model (GLMM) with binomially distributed errors was utilized to estimate effects of formaldehyde on AD symptoms. To account for serial correlations among repeated measurements, random effects were included in GLMM models for each subject. We adjusted for potential confounding factors, such as age, sex, day of the week (DOW), ambient $PM_{2.5}$, outdoor temperature and RH, indoor renovation within 2 years, purchase of new furniture or electronics within 1

year, SCORAD at enrollment, use of TCS, and presence of fever as a proxy of infection, when fitting the GLMM. In the GLMM, we also compared between with and without adjustment for ambient $PM_{2.5}$, temperature, and RH.

For subgroup analysis, we stratified the dataset by sex, age (< 6 years and ≥ 6 years), season, presence of parental allergic diseases, median value of body mass index (BMI) (≤ 16.8 kg/m^2 vs. > 16.8 kg/m^2), presence of indoor mold or dampness, and indoor environment conditions based on self-reported surveillance. Indoor temperature was stratified to 2 categories: ≤ 25.5°C vs. > 25.5°C by median value. RH was stratified to three categories: ≤ 40%, 41%–60%, and > 60%. We then fitted GLMM models to each dataset of subgroups and compared effect sizes between them. All results are expressed as percent change with 95% confidence intervals (CIs) of symptoms per increment of 10 ppb of formaldehyde concentration.

All procedures were conducted using R version 3.6.1 (The Comprehensive R Archive Network; http://cran.r-project.org). GLMMs were fitted using the "lme4" package (version 3.1.2). All tests were 2-sided. An alpha level less than 0.05 was considered significant.

RESULTS

Characteristics of AD patients and household environments

Table 1 shows the characteristics of subjects in the present study. A total of 4,789 person-days of symptom records were obtained from 55 subjects. Among them, 3,581 (74.8%) and 1,208 (25.2%) were recorded by boys and girls, respectively. The average age of the study subjects was 5.3 ± 4.2 years. The presence of AD symptoms was 53.7%, with higher frequencies found in boys (55.6%) than in girls (48.3%) (P < 0.0001). The average SCORAD at enrollment was 33.9 (standard deviation, 12.7).

Among 52 participants who responded to the questionnaire, parents of 25 (55.8%) had ever been diagnosed as having allergic diseases such as asthma, allergic rhinitis, or AD (**Table 2**).

Table 1. Characteristics of the subjects in this study

Characteristics	Total	Boys	Girls	*P* value*
No. of subjects	55	38 (69.1%)	17 (30.9%)	
Age (yr)	5.3 ± 4.2	5.2 ± 4.4	5.8 ± 3.8	0.619
Height (cm)	106.8 ± 29.6	106.3 ± 31.2	107.8 ± 25.6	0.856
Weight (kg)	21.6 ± 14.7	22.2 ± 16.3	20.2 ± 10.1	0.587
BMI (kg/m^2)	17.2 ± 2.6	17.6 ± 2.8	16.4 ± 1.7	0.072
SCORAD at enrollment	33.9 ± 12.7	34.3 ± 13.7	32.8 ± 9.9	0.656
Total IgE (U/L)	568.6 ± 917.6	603.0 ± 918.2	504.0 ± 941.0	0.726
Sensitization (%)				
Food allergens†	73.8	78.6	64.3	0.535
Inhalant allergens‡	42.9	47.8	33.3	0.644
No. of record (person-days)	4,789	3,581 (74.8%)	1,208 (25.2%)	
Presence of AD symptoms (%)	53.7	55.6	48.3	< 0.0001
Presence of fever (%)	3.1	1.5	7.9	< 0.0001
Use of TCS (%)	99.7	99.7	99.6	0.551

Data are expressed as mean ± standard deviation.
BMI, body mass index; SCORAD, SCORing of Atopic Dermatitis index at enrollment; TCS, topical corticosteroid.
*Test for differences between boys and girls: t-test for means of each variable, except symptom presence, fever, Use of TCS, and sensitization which were compared using the Mann-Whitney U test; †Sensitized by five allergens, including egg white, cow's milk, soybean, wheat, and peanut; ‡Sensitized by house dust mite (*Dermatophagoides pteronyssinus*, *D. farinae*).

Table 2. Characteristics of family and household

Variables	Number of response	Total (n = 55)	Boys (n = 38)	Girls (n = 17)
Presence of parental allergic diseases	52	29 (55.8)	12 (48.0)	7 (41.2)
Current smoking of parents	47	19 (40.4)	12 (38.7)	7 (43.8)
Indoor mold/dampness	51	6 (11.8)	3 (8.6)	3 (18.8)
Air purifier	51	45 (88.2)	30 (85.7)	15 (93.8)
Air conditioner	51	50 (98.0)	34 (97.1)	16 (100.0)
Indoor renovation within 2 years	50	18 (36.0)	12 (34.3)	6 (40.0)
New furniture or electronics within a year	51	30 (58.8)	21 (60.0)	9 (56.3)

Data are expressed as number (%).

Six (11.8%) out of 51 households had indoor mold or dampness. Most households had air purifiers (88.2%) and air conditioners (98.0%). In 19 (40.4%) out of 47 households, either the father or the mother was a smoker.

Average daily indoor temperature and RH during the study period were 25.3°C ± 2.3°C and 49.0% ± 12.0%, respectively (**Supplementary Table S1**). With respect to the outdoor environment, average temperature, RH, and PM_{10} were 14.2°C ± 10.4°C, 67.2% ± 15.2%, and 20.7 ± 12.8 μg/m^3, respectively.

Exposure assessment of indoor formaldehyde

The levels of indoor formaldehyde were compared after stratifying our patients according to their characteristics (**Table 3**). Overall, the mean concentration of indoor formaldehyde in the households of our patients was within the guideline level in Korea (100 μg/m^3). The average level of formaldehyde in 4,789 datasets was 13.6 ± 16.4 ppb. The highest concentration of indoor formaldehyde was observed in spring (18.1 ± 20.6 ppb), followed by that in summer (16.5 ± 21.0 ppb), fall (12.5 ± 13.5 ppb), and winter (10.8 ± 12.1 ppb). Indoor formaldehyde levels were higher in boys, in children under 6 years, in children with BMI ≤ 16.8 kg/m^2, and in children

Table 3. Summary of indoor formaldehyde levels and other environmental conditions

Classification	Subgroups	Number (person-days)	Formaldehyde* (ppb)	*P* value
All		4,789	13.6 ± 16.4	
Season	Spring	382	18.1 ± 20.6	-
	Summer	1,327	16.5 ± 21.0	0.096
	Fall	1,736	12.5 ± 13.5	< 0.0001
	Winter	1,344	10.8 ± 12.1	< 0.0001
Gender	Boys	3,581	15.0 ± 15.8	< 0.0001
	Girls	1,208	9.5 ± 17.5	
Age (yr)	< 6	3,118	14.4 ± 18.2	< 0.0001
	≥ 6	1,671	12.0 ± 12.5	
BMI (kg/m^2)	≤ 16.8	2,411	15.5 ± 18.6	< 0.0001
	> 16.8	2,378	11.7 ± 13.7	
Presence of parental allergic diseases	(−)	1,865	12.8 ± 14.4	< 0.0001
	(+)	2,631	15.1 ± 18.2	
Passive smoking	(−)	2,273	13.1 ± 18.2	< 0.0001
	(+)	1,699	15.5 ± 15.4	
Indoor mold/dampness	(−)	3,872	13.8 ± 17.1	< 0.0001
	(+)	617	16.4 ± 14.6	
Indoor temperature (°C)	≤ 25.5	2,429	12.3 ± 16.5	< 0.0001
	> 25.5	2,398	14.9 ± 16.3	
Indoor RH (%)	≤ 40	1,086	8.1 ± 11.2	-
	41–60	2,761	13.7 ± 14.8	< 0.0001
	> 60	942	19.6 ± 22.8	< 0.0001

Test for mean differences between subgroups except for season which was result from analysis of variance test.
BMI, body mass index; RH, relative humidity.
*The average concentration of formaldehyde presented as mean ± standard deviation.

with parental allergic diseases than in girls, children with age of 6 years or older, children with BMI over 16.8 kg/m^2, and children without family history ($P < 0.0001$), respectively. Houses with mold or dampness indoors showed higher formaldehyde concentrations than houses without ($P < 0.0001$). The higher level of formaldehyde was observed in children with smoking father or mother than in children whose parents were not smokers ($P < 0.0001$). Notably, indoor formaldehyde level increased as indoor temperature or RH increased.

Effects of formaldehyde on AD symptoms

Table 4 shows the effects of formaldehyde exposure on AD symptoms as a result of GLMM fitting after controlling for confounding factors including SCORAD at enrollment, fever, DOW, and use of TCS. Spline curves showed that there was linear relationships between AD symptoms and indoor formaldehyde (**Supplementary Fig. S2**). When ambient $PM_{2.5}$, temperature, and RH were controlled for, an increase in formaldehyde by 10 ppb was associated with 2.5% increase in AD symptoms as a whole, although such an increase in AD symptoms was not statistically significant. When patients were stratified into subgroups, the effects were statistically significant in spring and summer, showing higher effect sizes in spring. With an increase in formaldehyde by 10 ppb, AD symptom scores increased by 79.2% (95% CI, 19.6–168.4) in spring and by 39.9% (95% CI, 14.3–71.2) in summer when ambient $PM_{2.5}$, temperature, and RH were controlled for. AD symptom scores in children aged 6–18 years increased significantly by 28.0% (95% CI, 6.6–53.7) due to an increase in formaldehyde concentration by 10 ppb, whereas there was no increase in young children under 6 years. High indoor temperature was also a risk factor exacerbating adverse effects of formaldehyde on AD symptoms in children as shown in **Table 4**. When indoor temperature was over 25.5°C, an increase in formaldehyde by 10 ppb increased AD symptoms by 17.8% (95% CI, 3.9–33.6).

Table 4. Percent changes of atopic dermatitis symptoms caused by formaldehyde exposure

Classification	Subgroup	% change (95% CI)*
All		2.50 (−4.00, 9.45)
Season	Spring	79.18 (19.62, 168.37)†
	Summer	39.91 (14.33, 71.20)†
	Fall	−12.21 (−25.14, 2.96)
	Winter	−8.34 (−21.34, 6.79)
Gender	Boys	4.43 (−3.64, 13.18)
	Girls	1.44 (−9.84, 14.14)
Age (yr)	< 6.0	−1.37 (−8.01, 5.75)
	≥ 6.0	27.97 (6.58, 53.66)†
BMI (kg/m^2)	< 16.8	3.41 (−5.24, 12.84)
	> 16.8	4.28 (−6.13, 15.85)
Presence of parental allergic diseases	(−)	0.13 (−8.69, 9.80)
	(+)	4.92 (−4.77, 15.59)
Passive smoking	(−)	1.56 (−9.03, 13.38)
	(+)	2.47 (−6.32, 12.08)
Indoor mold/dampness	(−)	1.63 (−4.85, 8.56)
	(+)	29.84 (−1.03, 70.34)
Indoor temperature (°C)	< 25.5	−2.57 (−10.72, 6.33)
	> 25.5	17.8 (3.9, 33.55)†
Indoor RH (%)	< 40	−2.60 (−21.03, 20.14)
	40–60	−0.97 (−9.51, 8.39)
	> 60	14.17 (−0.87, 31.49)

CI, confidence interval; BMI, body mass index; RH, relative humidity.
*Percentage of change in AD symptoms per 10 ppb of formaldehyde exposure; †Statistically significant with 95% CI.

DISCUSSION

In the present longitudinal study, we assessed the effects of airborne formaldehyde exposed in real households on AD symptoms based on repeated measurements of formaldehyde concentrations using a real-time sensor device. The mean value of measured formaldehyde concentrations in our patients' houses was 13.6 ppb, which was much lower than the guideline level recommended by World Health Organization (WHO) in the year 2010 (0.1 mg/m^3 or 80 ppb).[23] Our data were similar to levels in European households under typical residential conditions for which average concentrations of formaldehyde were 16–24 ppb.[24]

In our study, we found that indoor airborne formaldehyde had a detrimental effect on AD symptoms in children, although indoor formaldehyde levels were within the allowable range. Indeed, the guideline of indoor formaldehyde by the WHO is considered to protect against both acute and chronic sensory irritations in the airways of the general population and to prevent cancer.[25,26] However, there is no known threshold of indoor formaldehyde, below which AD symptoms are not affected. It means that the WHO guideline does not reflect the safe level of formaldehyde exposure in patients with AD. Therefore, children with AD need to minimize exposure to even low concentrations of formaldehyde.

Indoor formaldehyde adversely affected AD symptoms in children, with statistical significance in spring and summer when formaldehyde levels were relatively high. These results are contrary to our expectations that indoor formaldehyde concentrations would increase in winter when there is generally less ventilation. On the other hand, high indoor temperature can lead to emission of formaldehyde from walls and furniture.[27] In our study, the highest indoor temperature was observed in summer (27.4°C ± 1.5°C), followed by spring (25.6°C ± 1.7°C) (**Supplementary Table S2**). The level of indoor formaldehyde is also affected by humidity.[21,22,26] For example, formaldehyde emissions from fiberglass filters and polyester filters used in building heating, ventilation, and air conditioning systems show marked increase with increasing humidity, up to 10 mg/h-m^2 at 80% RH.[28] Our study showed the same result. We found that formaldehyde levels were increased as indoor RH increased (**Table 3**). Considering that most (98.2%) households in the panel had air conditioners, there might be less ventilation during summer, additionally leading to a higher formaldehyde level compared to that in fall and winter. Taken together, our results showed that elevated concentrations of indoor formaldehyde in our panel contributed to the increase in percent change of AD symptoms by formaldehyde exposure when indoor temperature was over 25.5°C and RH was over 60%, especially during spring and summer.

Cigarette smoke is a well-known source of indoor air pollutants. Numerous toxic constituents are released by burning cigarettes. Human health is adversely affected not only for active smokers, but also for nonsmokers who are exposed to second-hand and third-hand smoke. In other words, harmful effects are caused by environmental tobacco smoke (ETS) which comes from mainstream smoke, side-stream smoke emitted from puffs, and residual smoke absorbed on the surfaces of indoor furnishings or clothing. Because cigarette smoking also leads to pollution of the room air with formaldehyde,[29] it is not surprising that indoor formaldehyde concentrations are higher in households with smokers than those without in the present study ($P < 0.0001$). Behaviors or life styles of smokers may also influence a high indoor formaldehyde level. However, we could not find a significant effect of formaldehyde on AD symptoms in the subgroup with parental smoking, although the indoor formaldehyde level was high. Although the reason was unclear, the average concentration of indoor

formaldehyde in households with parental smoking was 15.5 ± 15.4 ppb. It might not be high enough to irritate the skin. Indeed, this level was lower than 18.1 ± 20.6 ppb in spring and 16.5 ± 21.0 ppb in summer when formaldehyde appeared to affect AD.

Of note, we observed that children aged over 6 years showed a significant increase in percent change of AD symptoms by exposure to formaldehyde, whereas those under 6 years did not. Given that formaldehyde concentration was lower in the households of patients aged over 6 years than in those of patients aged under 6 years, our finding was not caused by exposure to higher doses of formaldehyde. Rather, it may be explained by different sensitivities to formaldehyde. Actually, there was a difference in AD severity between the 2 groups. The SCORAD at enrollment for children aged over 6 years was higher than that for children under 6 years (40.1 ± 14.6 vs. 30.4 ± 10.4; $P = 0.012$). After all, children over 6 years with more severe symptoms are likely to be more vulnerable to formaldehyde even at lower concentrations than children under 6 years of age with mild symptoms. In addition to AD severity, the harmful effect of formaldehyde may vary due to differences in exposure amount, route, or source. However, we did not identify those factors in the present study.

To the best of our knowledge, this is the first longitudinal study demonstrating an adverse effect of formaldehyde on AD based on regular monitoring of clinical symptoms and continuous assessment of household exposure. The strength of our study was that we observed the impact of airborne formaldehyde on human patients in a real-life situation. Our study design is quite different from previous animal experiments[30-33] or provocation tests in humans in that those studies exposed formaldehyde artificially without evaluating clinical symptoms.[17,18] Our research was based on personal monitoring of indoor air pollutant levels and AD symptoms in a longitudinal way. Recent sensor and communication technologies enabled us to measure real-time formaldehyde concentration in households of each patient and automatically transfer those data.[34] Consequently, we found that AD symptoms of pediatric patients were adversely affected by exposure to airborne formaldehyde even at low concentrations within allowable range.

This study has some limitations. We had more data from boys than from girls. It could make a biased result, and sex difference should be carefully considered in the interpretation of our results. However, when we analyzed the effect of indoor formaldehyde according to sex, the results were not significant in either group (**Table 4**). Furthermore, when we included 'sex' in the model as a confounding factor, the effect of sex was not significant ($P = 0.345$ in cases of overall model). Secondly, we did not measure the level of outdoor formaldehyde. However, formaldehyde mainly comes from indoor materials, and the outdoor formaldehyde level is less than the indoor level.[23] Therefore, if any, outdoor formaldehyde might not play an important role. Thirdly, the number of our study population was small and their daily activities (indoors and outdoors) were not checked. Finally, there was an issue about the accuracy of formaldehyde concentrations. Although the SSGSM-HCHO sensor used in this study showed excellent linear response (**Supplementary Fig. S1**) compared to Interscan 4000 (Interscan Co., Chatsworth, Canada) widely used to measure indoor formaldehyde concentration,[35] it was not a standard measuring instrument. In addition, this device was placed only in the living room. Despite these limitations, we have obtained clinically significant results with regard to indoor formaldehyde at the level that we are commonly exposed to in our daily lives.

In conclusion, indoor formaldehyde can exacerbate AD symptoms in children with moderate-to-severe severity, particularly in spring and summer, even when its concentration is low at home. Indoor formaldehyde level can be altered by other environmental factors such as

temperature and humidity. Thus, minimizing exposure to indoor formaldehyde may be needed for the proper management of AD in children.

ACKNOWLEDGMENTS

This research was supported by R&D Center for Green Patrol Technologies through R&D for Global Top Environmental Technologies funded by Ministry of Environment (MOE), Republic of Korea.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Summary of indoor and outdoor environments

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Supplementary Table S2

Indoor temperature by season during study period

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Supplementary Fig. S1

Comparison of the formaldehyde concentrations measured by SSGSM-HCHO with those by Interscan 4000.

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Supplementary Fig. S2

Relationship of environmental risk factors with atopic dermatitis symptoms. Each figure shows the spline curve (solid lines) with a 95% confidence interval (2 dashed lines). The model was controlled for the severity score at the initial visit, age, sex, presence of fever, and day of week.

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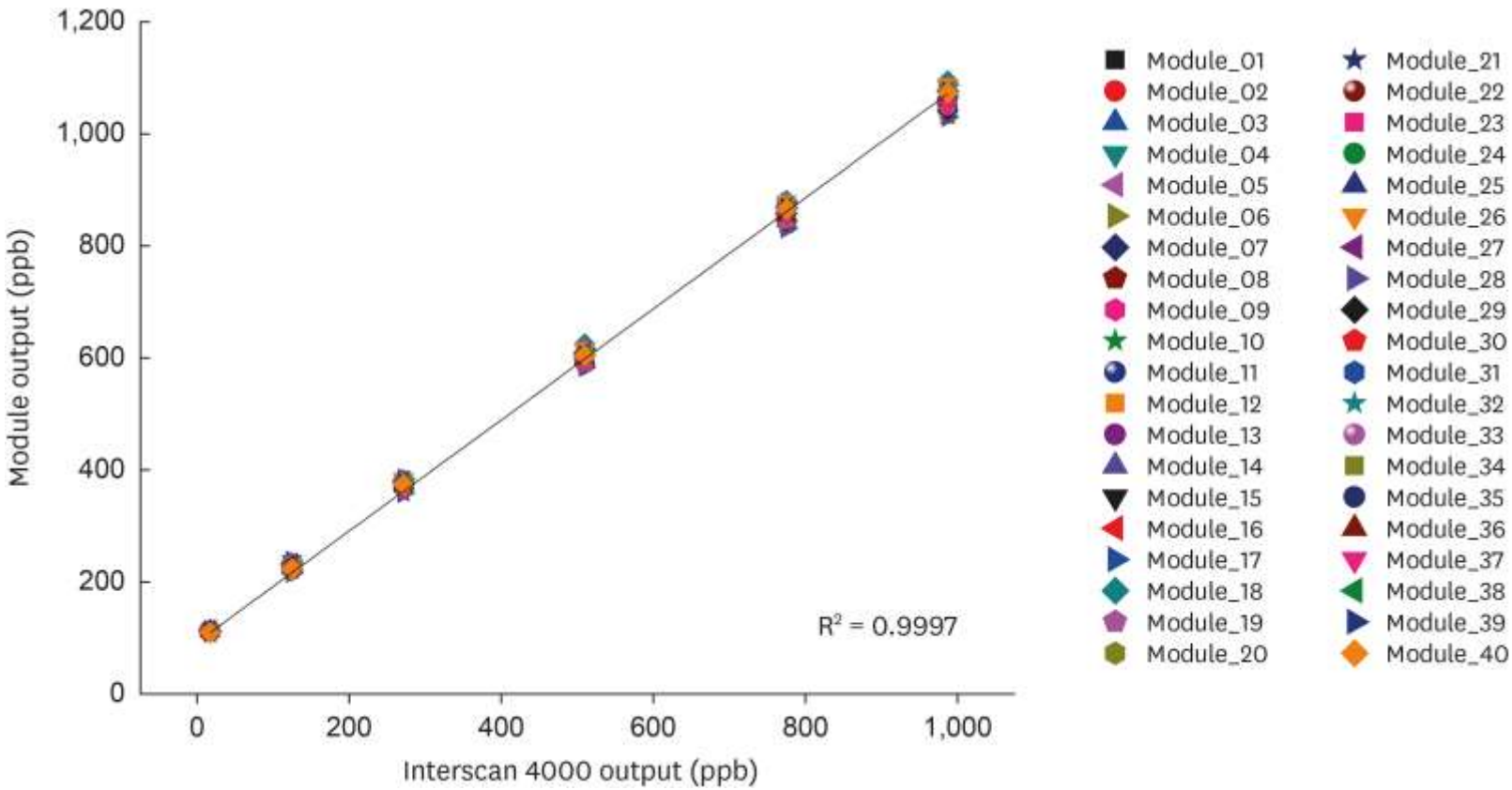

Supplementary Fig. S1. Comparison of the formaldehyde concentrations measured by SSGSM-HCHO with those by Interscan 4000. The assessment of SSGSM-HCHO (SENKO, Osan, Korea) was performed in the chamber with the size of 8 m3. The formaldehyde, purchased from Daejung Chemical Reagent Co. (Siheung, Korea), was vaporized and supplied into the chamber by bubbling . . .

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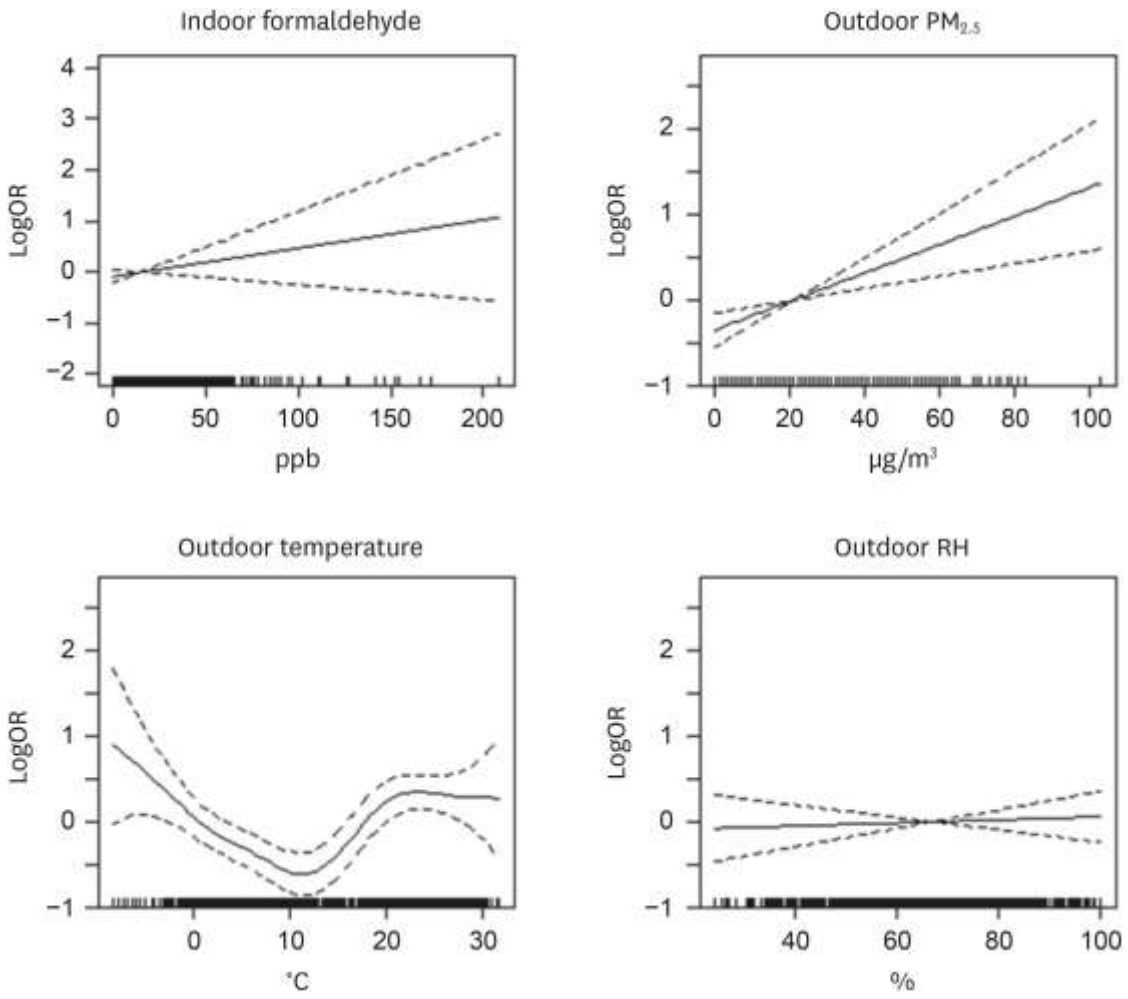
https://doi.org/10.4168/aair.2021.13.3.468



Supplementary Fig. S2. Relationship of environmental risk factors with atopic dermatitis symptoms. Each figure shows the spline curve (solid lines) with a 95% confidence interval (2 dashed lines). The model was controlled for the severity score at the initial visit, age, sex, presence of fever, and day of week. . .

Allergy Asthma Immunol Res. 2021 May;13(3):468-478.
https://doi.org/10.4168/aair.2021.13.3.468