

Exposure to Gene-Environment Interactions before 1 Year of Age May Favor the Development of Atopic Dermatitis

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Key Words

Atopic dermatitis · Gene-environment interaction · Prevalence · Risk factor

Abstract

Background: The aims of this study were to determine (1) the prevalence of atopic dermatitis (AD) in Seoul, Korea, and (2) the influence of environmental and genetic factors on disease risk. **Methods:** A questionnaire survey was conducted in 5,036 primary school children and 4,607 middle school children in 2008. For each child, a modified version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and a questionnaire assessing exposure to environmental variables were completed. **Results:** In primary school children, the lifetime prevalence of itchy eczema was 24.3%, the 12-month prevalence of itchy flexural eczema was 18.0%, the lifetime prevalence of AD diagnosis was 31.3%, and the 12-month prevalence of AD treatment was 14.5%. In middle school children, the corresponding

rates were 16.0, 10.8, 22.1, and 8.3%, respectively. These rates are significantly higher than those reported in similar studies conducted in 1995 and 2000. In both primary and middle school children, a parental history of allergic disease and a history of having moved into a newly built house before 1 year of age were independently associated with a risk for current AD. For current AD, the prevalence odds ratio was higher in the subgroup with both a genetic and a specific environmental risk factor than in the subgroup with no risk factor or subgroups with only one risk factor. **Conclusions:** The prevalence of AD in primary and middle school children in Seoul has increased. Its development may be influenced by gene-environment interactions, particularly before 1 year of age.

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Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease which often occurs in association with asthma and allergic rhinitis. More than 50% of all AD patients will eventually develop asthma, and two thirds will develop allergic rhinitis [1, 2]. This sequential development of allergic diseases is termed 'the atopic march' [1, 3]. Thus, AD is often the first symptom of allergic disease. The prevalence of AD has increased significantly over the last three decades, particularly in developed countries, and the disease currently affects around 20–30% of children [4–8]. Two Nationwide Studies of Asthma and Allergies in Korean Children have been conducted, the first in 1995 and the second in 2000. Both applied the methods formulated by the International Study of Asthma and Allergies in Childhood (ISAAC) [9]. The 12-month prevalence of itchy flexural eczema in primary school children was 7.3% in 1995 and 10.7% in 2000, demonstrating a definite trend toward an increase in the lifetime prevalence of AD [10, 11].

Although the pathogenesis of AD remains unclear, the disease appears to result from a complex interaction between genetic and environmental factors. These include various susceptibility genes, defects in skin barrier function, immune responses and infectious agents. Recent research has indicated that environmental influences in early life play a key role in epigenetic mechanisms [12, 13].

The aims of the present study were (1) to determine the prevalence of AD in primary and middle school children in Seoul, Korea, and (2) to investigate the influence of a genetic and environmental interaction on the development of AD, especially before 1 year of age.

Materials and Methods

Subjects

A cross-sectional study was conducted in children from two age groups: (1) 6- to 11-year-olds (primary school children) and (2) 12- to 14-year-olds (middle school children). A total of 5,036 primary school children and 4,607 middle school children were recruited from five schools. These schools had been randomly selected from five different districts of Seoul, Korea (downtown, northeast, northwest, southeast and southwest). A total of 4,731 primary school and 4,337 middle school children and their parents responded to the study questionnaires, which made up an overall response rate of 93.9 and 94.1%, respectively. Cases in which sex had not been reported were excluded, which meant the responses of a total of 4,554 primary school and 4,090 middle school children and their parents were included in the analyses. The mean age was 9.45 ± 1.73 years in primary school children and 13.83 ± 0.98 years in middle school children. The primary

Table 1. Subject characteristics

	Primary school children	Middle school children
Surveyed	5,036	4,607
Response rate, %	93.9	94.1
Total	4,731	4,337
Analyzed	4,554	4,090
Age, years	9.45 ± 1.73	13.83 ± 0.98
Sex		
Males	2,317 (50.9%)	1,661 (40.6%)
Females	2,237 (49.1%)	2,429 (59.4%)
BMI	17.90 ± 3.14	19.78 ± 3.02
Maternal education, %		
Primary/middle school	2.2	3.2
High school	37.0	36.6
University	60.8	60.1
Parental income, monthly, %		
Low, ≤ 1.99 million KRW	13.3	11.7
Middle, 2–3.99 million KRW	49.7	41.1
High, ≥ 4 million KRW	37.0	47.2
Parental allergic disease, %	37.7	43.6
Household pets, %	8.2	14.2
Day care attendance, %	90.5	83.6
Moving into a newly built house ever, %	41.0	48.3
Moving into a newly built house before 1 year of age, %	12.9	12.8
Mold in the house when the child was less than 1 year old, %	10.3	6.5
Mold in the house during the last 12 months, %	14.2	11.0

BMI = Body mass index; KRW = South Korean won.

school sample included 2,317 boys and 2,237 girls (boys:girls = 50.9:49.1). The middle school sample included 1,661 boys and 2,429 girls (boys:girls = 40.6:59.4) (table 1).

Data Collection

Data on physical examination findings and questionnaire responses were collected between May and October 2008. All study procedures, including collection of the questionnaires, were conducted by trained researchers under the supervision of a pediatric allergy specialist, who conducted the physical examinations. The Korean versions of the ISAAC questionnaire and the environmental questionnaire were used [9]. The two study questionnaires were comprised of items that investigated three main areas: (1) general characteristics including name, sex, date of birth, height and weight; (2) a history of symptoms suggestive of asthma, allergic rhinitis, AD, allergic conjunctivitis and food allergy as in the original ISAAC questionnaire, and (3) environmental factors associated with allergic disease. Some of these items focused specifically on their history before 1 year of age. The Korean version of the ISAAC questionnaire was completed by parents in the case

Table 2. Comparison of prevalence of AD in Seoul, Korea, between 1995, 2000 and 2008

Year	1995 ¹	2000 ¹	2008
Primary school children			
Itchy eczema, ever	18.2 (17.4–19.1)	18.9 (18.0–19.8)	24.3 (23.6–25.0)
Itchy flexural eczema, last 12 months	8.8 (8.2–9.5)	12.0 (11.3–12.8)	18.0 (17.4–18.6)
Diagnosis of AD, ever	19.7 (18.8–20.6)	27.5 (26.5–28.5)	31.3 (30.6–32.0)
Treatment of AD, last 12 months	9.3 (8.7–10.0)	13.5 (12.7–14.2)	14.5 (14.0–15.0)
Current AD ²	–	–	14.2 (13.7–14.7)
Middle school children			
Itchy eczema, ever	8.7 (7.9–9.6)	10.0 (9.0–10.8)	16.0 (15.4–16.6)
Itchy flexural eczema, last 12 months	4.9 (4.3–5.6)	6.3 (5.5–7.0)	10.8 (10.3–11.3)
Diagnosis of AD, ever	7.6 (6.8–8.4)	13.5 (12.5–14.6)	22.1 (21.4–22.8)
Treatment of AD, last 12 months	4.6 (4.0–5.3)	8.4 (7.5–9.2)	8.3 (7.9–8.7)
Current AD ²	–	–	8.0 (7.6–8.4)

Figures in parentheses are 95% CIs.

¹ Extracted from the Nationwide Study of Asthma and Allergies in Korean Children [9, 10].

² Current AD = A lifetime history of AD diagnosis and a 12-month history of itchy flexural eczema.

of all primary school children and by self-reporting for the middle school children. The environmental questionnaire was completed exclusively by parents. The study was approved by the Institutional Review Board of Asan Medical Center. Written consent was obtained from all parents and guardians following a detailed explanation of the study.

Statistical Analysis

All statistical analyses were performed using SPSS software 14.0 (SPSS Inc., Chicago, Ill., USA). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression analysis. In gene-environmental interaction, the analyses were composed of a cross-tabulation according to the presence or absence of the genetic factor and one of the two environmental factors. The prevalence OR was derived from this cross-tabulation analysis. A *p* value <0.05 was considered statistically significant. We adjusted age, sex, and BMI as personal factors, parental allergic disease as familial factor and parental income as socioeconomic factor in multivariate analysis.

Results

General Characteristics

The prevalence of a parental history of allergic disease (including AD, asthma and allergic rhinitis) which had been diagnosed previously by a doctor was 37.7% in primary school children and 43.6% in middle school children. A positive history of having moved into a newly built house during the period younger than 1 year old was reported in 12.9% of primary school children and 12.8% of middle school children. The presence of mold in the house during the period younger than 1 year old was re-

ported in 10.3% of primary school children and 6.5% of middle school children (table 1).

Prevalence of AD

In primary school children, the lifetime prevalence of itchy eczema was 24.3%, the 12-month prevalence of itchy flexural eczema was 18.0%, the lifetime prevalence of AD diagnosis was 31.3%, and the 12-month prevalence of AD treatment was 14.5%. The corresponding rates in previous studies were 18.2, 8.8, 19.7, and 9.3% in 1995, and 18.9, 12.0, 27.5, and 13.5% in 2000 [14].

In middle school children, the lifetime prevalence of itchy eczema was 16.0%, the 12-month prevalence of itchy flexural eczema was 10.8%, the lifetime prevalence of AD diagnosis was 22.1%, and the 12-month prevalence of AD treatment was 8.3%. The corresponding rates in previous studies were 8.7, 4.9, 7.6, and 4.6% in 1995, and 10.0, 6.3, 13.5, and 8.4% in 2000. AD prevalence was compared between 1995, 2000, and 2008 (table 2). Data for 1995 and 2000 were extracted from previous studies [10, 11]. In 2008, the prevalence of AD in primary school and middle school children was significantly higher than in 1995 and 2000, with the exception of the 12-month prevalence of AD treatment in middle school children, which did not differ significantly between 2000 and 2008.

Current AD was defined as a lifetime history of AD diagnosis and a 12-month history of itchy flexural eczema. The prevalence of current AD was 14.2% in primary school children and 8.0% in middle school children.

Table 3. Univariate analysis of possible risk factors for current AD

Variable	Primary school children		Middle school children	
	OR	p value	OR	p value
Sex, female	1.034 (0.874–1.224)	0.696	1.797 (1.399–2.308)	<0.001
Prematurity	0.783 (0.514–1.191)	0.251	1.209 (0.622–2.347)	0.575
Parental allergic disease	1.715 (1.430–2.056)	<0.001	1.506 (1.115–2.033)	0.007
Maternal education	1.224 (1.040–1.441)	0.025	0.927 (0.735–1.168)	0.520
High school	2.350 (1.016–5.437)	0.046	1.168 (0.525–2.597)	0.704
University	2.707 (1.177–6.228)	0.019	1.038 (0.471–2.287)	0.927
Parental monthly income	1.107 (0.971–1.261)	0.128	0.970 (0.813–1.159)	0.739
Middle, 2–3.99 million KRW	1.114 (0.843–1.472)	0.447	0.984 (0.660–1.465)	0.935
High, ≥4 million KRW	1.229 (0.924–1.634)	0.157	0.948 (0.639–1.405)	0.789
BMF	1.037 (0.875–1.230)	0.673	0.981 (0.770–1.251)	0.879
BMF for ≥4 months	0.859 (0.719–1.028)	0.097	1.004 (0.779–1.294)	0.973
Bronchiolitis before 2 years of age	1.452 (1.140–1.850)	0.002	0.818 (0.516–1.296)	0.391
Day care attendance	1.193 (0.881–1.617)	0.254	1.221 (0.866–1.721)	0.254
Day care attendance before 1 year of age	1.016 (0.687–1.501)	0.938	1.319 (0.654–2.660)	0.438
Vaccination	1.267 (0.813–1.974)	0.294	1.105 (0.620–1.971)	0.735
BCG	1.310 (0.773–2.221)	0.314	0.945 (0.599–1.490)	0.808
Sibling history of measles	1.223 (0.861–1.737)	0.260	0.967 (0.588–1.590)	0.894
Exposure to smoking	1.149 (0.968–1.365)	0.112	0.962 (0.754–1.227)	0.753
Smoking during pregnancy	0.662 (0.084–5.236)	1.000	5.603 (0.507–61.98)	0.227
Ingestion of probiotics before 1 year of age	1.075 (0.888–1.301)	0.460	1.030 (0.781–1.357)	0.834
Ingestion of vitamins before 1 year of age	1.029 (0.821–1.291)	0.803	1.238 (0.913–1.678)	0.169
Moving into a newly built house, ever	1.194 (1.007–1.416)	0.041	1.165 (0.885–1.532)	0.276
Moving into a newly built house before 1 year of age	1.535 (1.221–1.929)	<0.001	1.787 (1.255–2.544)	0.001
Mold in the house when the child was less than 1 year old	1.470 (1.126–1.918)	0.004	3.710 (2.599–5.295)	<0.001
Mold in the house during the last 12 months	1.555 (1.237–1.954)	<0.001	1.371 (0.946–1.986)	0.094
Household pets	0.928 (0.678–1.269)	0.640	0.934 (0.655–1.333)	0.708
Pets from pregnancy to less than 1 year of age	1.285 (0.869–1.899)	0.208	1.415 (0.724–2.766)	0.307
Home located near a factory	0.923 (0.649–1.313)	0.655	0.825 (0.396–1.716)	0.606

Figures in parentheses are 95% CIs. BMF = Breast milk feeding; KRW = South Korean won; BCG = bacille Calmette-Guérin.

Risk Factors for AD

Univariate Logistic Regression

In the univariate logistic regression analyses for current AD, eight out of 50 variables reached statistical significance in primary school and/or middle school children (table 3). Possible risk factors for current AD in both primary and middle school children were: a parental history of allergic disease, a history of having moved into a newly built house during the period younger than 1 year

old, and the presence of mold in the house during the period younger than 1 year old. In primary school children, possible risk factors for current AD also included: a higher level of maternal education, a history of bronchiolitis before the age of two, a lifetime history of having moved into a newly built house, and the presence of mold in the house during the previous 12 months. In middle school children, a further possible risk factor for current AD was female sex.

Table 4. Multivariate analysis of possible risk factors for current AD

Variable	Primary school children		Middle school children	
	aOR	p value	aOR	p value
Sex, female	1.158 (0.939–1.429)	0.170	1.644 (1.110–2.459)	0.015
Parental allergic disease	1.710 (1.388–2.106)	<0.001	1.650 (1.161–2.345)	0.005
Maternal education	1.202 (0.970–1.490)	0.092	0.753 (0.539–1.054)	0.098
High school	2.112 (0.750–5.950)	0.157	1.242 (0.421–3.664)	0.694
University	2.411 (0.857–6.783)	0.095	0.845 (0.280–2.549)	0.764
Parental monthly income	0.998 (0.844–1.179)	0.977	1.111 (0.839–1.471)	0.461
Middle, 2–3.99 million KRW	1.029 (0.725–1.462)	0.871	1.585 (0.845–2.970)	0.151
High, ≥4 million KRW	1.013 (0.701–1.464)	0.946	1.462 (0.761–2.809)	0.254
Bronchiolitis before the age of 2	1.384 (1.031–1.856)	0.030	1.162 (0.630–2.144)	0.630
Moving into a newly built house, ever	1.104 (0.891–1.368)	0.367	1.382 (0.941–2.030)	0.099
Moving into a newly built house before 1 year of age	1.420 (1.062–1.898)	0.018	2.078 (1.300–3.323)	0.002
Mold in the house when the child was less than 1 year old	1.287 (0.917–1.807)	0.145	2.828 (1.652–4.843)	<0.001
Mold in the house during the last 12 months	1.351 (1.005–1.815)	0.046	1.205 (0.677–2.147)	0.526

Figures in parentheses are 95% CIs. KRW = South Korean won.

Multivariate Logistic Regression

Although the significance of the possible risk factors was slightly lower in the multivariate logistic regression than in the univariate logistic models, the ORs were generally consistent (table 4). In both primary and middle school children, a parental history of allergic disease [OR adjusted for age, sex, BMI, parental allergic disease, maternal education and parental income (aOR, 1.710; 95% CI, 1.388–2.106 in primary school children and aOR, 1.650; 95% CI, 1.161–2.345 in middle school children], and a history of having moved into a newly built house during the period younger than 1 year old (aOR, 1.420; 95% CI, 1.062–1.898 in primary school children and aOR, 2.078; 95% CI, 1.300–3.323 in middle school children) were independently associated with the risk for current AD. In primary school children, a history of bronchiolitis before the age of 2 years (aOR, 1.384; 95% CI, 1.031–1.856) and the presence of mold in the house during the last 12 months (aOR, 1.351; 95% CI, 1.005–1.815) were both associated with an increased risk for current AD. In middle school children, female sex (aOR, 1.644; 95% CI, 1.110–2.459) and the presence of mold in the house during the period younger than 1 year old (aOR, 2.828; 95% CI, 1.652–4.843) were both associated with an increased risk for current AD.

Gene-Environment Interaction

Analyses were performed to determine whether an interaction between genetic factors (a parental history of allergic disease) and environmental factors (a history of having moved into a newly built house during the period younger than 1 year old or the presence of mold in the house during the period younger than 1 year old) was implicated in the development of AD. Each primary and middle school group was divided into four subgroups according to the presence or absence of two risk factors (the genetic factor and one of the two environmental factors).

The prevalence OR (POR) for current AD was significantly higher in the subgroup with both a genetic and a specific environmental risk factor than in the subgroup with no risk factors in both primary and middle school children. And the POR was higher in subgroups with both a genetic and a specific environmental risk factor than in subgroups with only one risk factor. For a parental history of allergic disease and a history of having moved into a newly built house during the period before 1 year of age, the PORs increased in primary school children from 1.663 (95% CI, 1.358–2.035) and 1.331 (95% CI, 0.919–1.927) with only one risk factor, to 3.059 (95% CI, 2.176–4.300) with both risk factors. Meanwhile, in middle school children, the PORs increased from 1.572 (95% CI, 1.093–2.261) and 2.164 (95% CI, 1.188–3.942) with

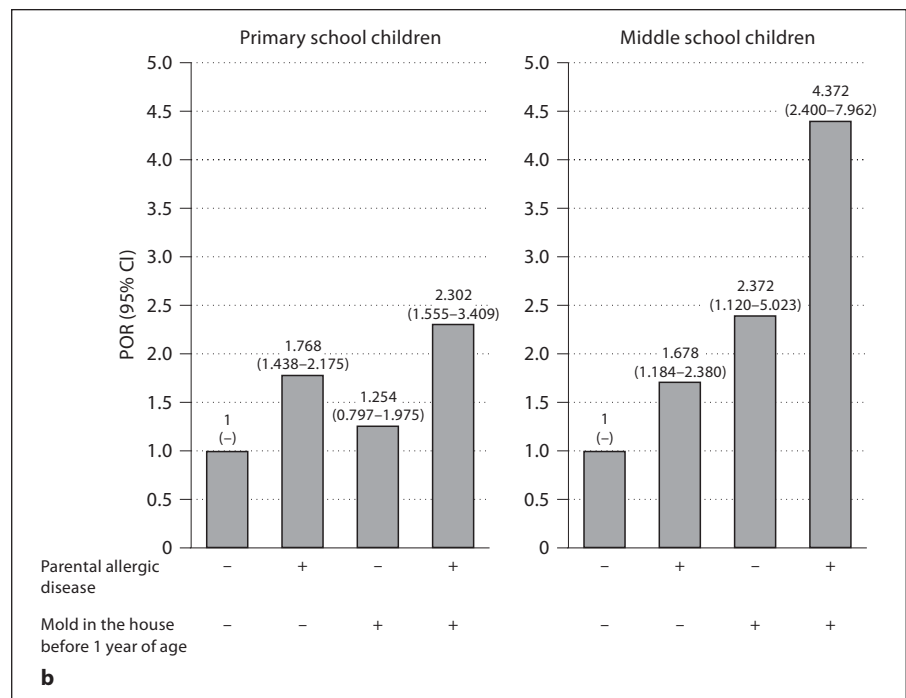
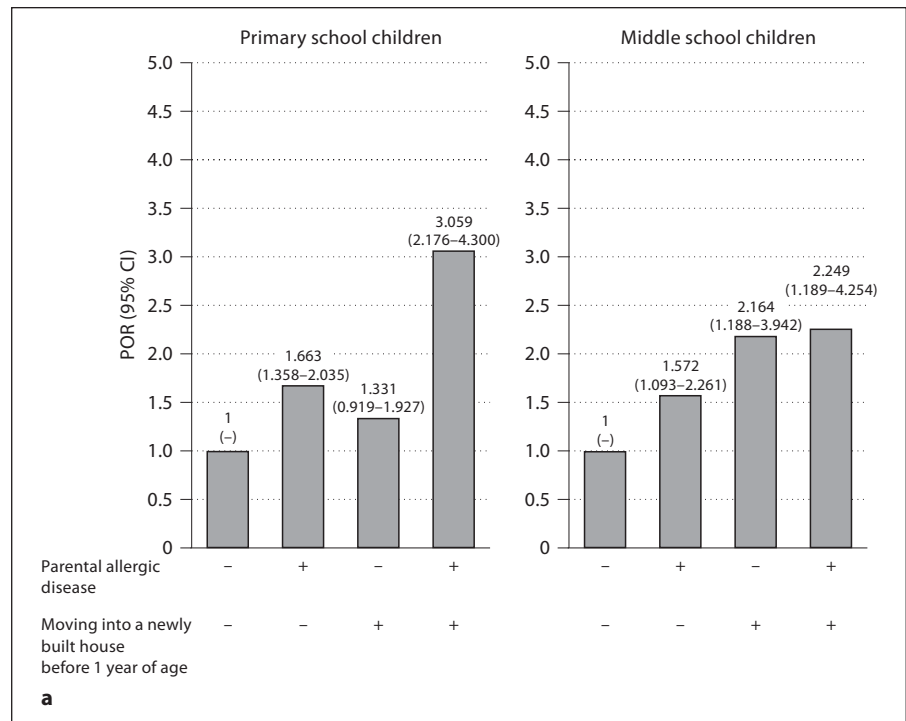


Fig. 1. POR for current AD was found to increase with an increasing number of specific risk factors. **a** Parental history of allergic disease and a history of having moved into a newly built house before 1 year of age. **b** Parental history of allergic disease and presence of mold in the house when the child was less than 1 year old.

only one risk factor, to 2.249 (95% CI, 1.189–4.254) with both risk factors. For a parental history of allergic disease and the presence of mold in the house during the period before 1 year of age, the PORs in primary school children rose from 1.768 (95% CI, 1.438–2.175) and 1.245 (95% CI,

0.797–1.975) with only one risk factor, to 2.302 (95% CI, 1.555–3.409) with both risk factors. In middle school children, the PORs rose from 1.678 (95% CI, 1.184–2.380) and 2.372 (95% CI, 1.120–5.023) with only one risk factor, to 4.372 (95% CI, 2.400–7.962) with both risk factors (fig. 1).

Discussion

The present study has demonstrated that the prevalence of AD among primary and middle school children in Seoul, Korea has increased over the past 13 years. It has also identified specific risk factors for the development of AD. Children with a genetic susceptibility to AD, defined as a parental history of allergic disease, were more likely to present with AD when they had a history of exposure to environmental risk factors, particularly before 1 year of age.

In the present study, the prevalence of current AD was 14.2% in primary school children and 8.0% in middle school children. The prevalence of AD in Seoul, Korea is thus similar to that reported in Western countries in studies that have applied the ISAAC questionnaire [15, 16]. The 12-month prevalence of itchy flexural eczema in Seoul was significantly higher in 2008 than in 1995 and 2000, demonstrating that the prevalence of AD continues to increase [10, 11]. This upward trend is more pronounced in industrialized countries [4–8]. Seoul underwent rapid industrialization in the 1960s, and children in the city have subsequently been exposed to an increasing array of environmental factors. The steep increase in AD prevalence thus appears to reflect the importance of environmental risk factors in the development of this disease.

The risk factor analyses implicated both genetic and environmental factors in the development of AD. The findings on a parental history of allergic disease, which has been identified as one of the strongest risk factors in numerous studies, provide support for the hypothesis that genetic factors influence the development of AD [17, 18]. Genetic factors have been implicated in the familial aggregation of various diseases, including AD [19, 20]. The present study has highlighted the importance of the home environment as a potential environmental risk factor. Although research into the effects of indoor air pollution is scarce, mold has been identified as one potential cause of asthma [21, 22]. The association between mold and AD was reported in previous studies. Several studies have reported a positive association between mold and AD [23–26]; another study in Germany suggested mold is not related with atopic eczema [27]. Sick building syndrome is a syndrome associated with an individual's place of work or residence. In 1984, the World Health Organization suggested that up to 30% of new and remodeled buildings worldwide may be linked to symptoms of sick building syndrome. Most of the sick building syndrome is related to poor indoor air quality. With regard

to moving into a newly built house, studies in Japan have recently identified chemical substances emitted from indoor building materials, such as formaldehyde and volatile organic compounds as major causes of sick building syndrome [28, 29]. These chemicals may thus increase the risk of allergic disease [30] and several studies reported a correlation between AD and sick building syndrome [31, 32].

A major focus of the present study was to analyze interactions between genetic and environmental risk factors. Its findings suggest that the development of AD results from gene-environment interactions rather than from the effects of either genetic or environmental factors alone. To our knowledge, this is the first study to have applied the simple approach of calculating POR to the investigation of AD. It reports results of statistical analyses which have an observational character. Indeed, additional experimental studies, such as the direct measurement of fungal exposure in a cohort study or animal study of fungal exposure, would be helpful and are needed to verify and to better understand these observations in the future.

Interestingly, the environmental factors identified by the present study had a more significant influence on the development of AD when exposure had occurred before 1 year of age. Previous studies have shown that early allergen exposure plays an important role in the development of allergic disease [33, 34]. One proposed hypothesis for this is that an interaction between genotype and exposure to an environmental risk factor during infancy influences the development of the immune system and results in a predisposition to allergic disease [35, 36]. This epigenetic mechanism is a key aspect of the 'developmental origins of health and disease' hypothesis [12, 13]. Environmental modifications are needed for the primary prevention of AD [37].

The present study included relatively large sample sizes and achieved a high response rate. It was designed by a researcher who had participated in the 1995 and 2000 Korean ISAAC studies, and the questionnaires were essentially similar to those used previously [10, 11]. The environmental questionnaire was modified in order to yield more information on environment influences. The limitation of the study is that comparison of the ISAAC questionnaires between primary school and middle school children was complicated by the different methods of reporting. In addition, an exact causal relationship between environmental factors and the results (symptoms of AD) can not be suggested because this was a cross-sectional study. But a cause-and-effect relationship can be suggested

ed. Further additional prospective cohort studies are therefore required.

In conclusion, the prevalence of AD among primary and middle school children in Seoul, Korea, continues to increase. The development of AD may be determined by gene-environment interactions, and the first year of life may be a critical period in this process. Minimizing exposure to possible environmental risk factors in infants with a genetic susceptibility should therefore contribute to a reduction in the prevalence of AD.

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Disclosure Statement

The authors have no conflict of interests or financial arrangements pertaining to this article to declare.

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