Risk factors of atopic dermatitis in Korean schoolchildren: 2010 international study of asthma and allergies in childhood

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Summary

Background & Objective: **We aimed to analyse the risk factors of atopic dermatitis (AD) in Korean schoolchildren in 2010.**

Methods: **A nationwide, cross-sectional study was conducted in children aged 6-7 years and adolescents aged 12-13 years who were randomly selected. Information was obtained through a Korean version of the International Study of Asthma and Allergies in Childhood questionnaire (ISAAC), and skin prick tests were performed. AD-diagnosed children were selected for risk factor analysis by using logistic regression.**

Results: **We enrolled 4,003 children (M/F=2,021/1,982) in aged 6-7 years and 4,112 children (M/F=2,029/2,083) in 12-13 years. In children aged 6-7 years, the lifetime prevalence of AD diagnosis was 35.6% (N=1,424). On the other hand, in the 12 to 13 year age group, the lifetime prevalence of AD diagnosis was 24.2% (N=981). In the univariate logistic regression analysis in 6-7 year-old children, possible risk factors were atopy, a parental history of allergic disease, the use of antibiotics during infancy, a history of having moved into a newly built house during infancy, the presence of visible mould in the house, and remodelling of house within 12 months. The statistical significance persisted after adjustment. However, antibiotic use during infancy and remodelling within 12 months showed no statistical significance as a risk factor for AD. In contrast, multivariate logistic regression analysis in adolescents demonstrated that female sex, atopy, a parental history of allergic diseases, the presence of visible mould in the house, and a history of having moved into a newly built house during infancy was associated with AD. There was no significant association between AD and other risk factors.**

Conclusion: **In Korean schoolchildren, risk factors such as atopy, the presence of parental allergic diseases, moving into a newly built house during infancy and visible mould in the house were associated with AD. *(Asian Pac J Allergy Immunol 2016;34:65-72)***

Keywords: *Atopic dermatitis; ISAAC; risk factors, schoolchildren, newly built house*

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Introduction

Atopic dermatitis (AD) is one of the most common chronic diseases in children and adolescents. AD is caused by a combination of genetic and environmental factors, and presents with various symptoms and signs such as pruritus, dry skin, and erythema.

The International Study of Asthma and Allergies in Childhood (ISAAC), which started in the 1990s,[1] has provided valuable data on the prevalence and potential risk factors of symptoms of asthma, allergic rhinoconjunctivitis and AD.[2, 3] It has also compared the prevalence among the different countries and showed the time trend in each region.[4-7] As a result of various studies based on ISAAC, the incidence of AD in the infant population was estimated to be 15–20%, showing an increase in prevalence.[8] Particularly, a continuous increasing prevalence of AD and subsequent rise in AD medication use has been reported in developed countries.[9] In Korea, nationwide surveys using the ISAAC questionnaire were conducted twice, in 1995 and 2000,[10] and the 3rd nationwide survey on childhood AD was performed in 2010.

For primary, secondary and tertiary prevention of childhood AD, it is crucial to determine the risk factors which are responsible for the development or exacerbation of AD. The presence of asthma or rhinitis symptoms and a positive family history for allergic diseases are linked to the incidence of AD.[11] In addition, several environmental factors, such as indoor allergens[12] and environmental tobacco smoke (ETS),[13] have a relevant influence on the development of AD. Dietary factors, such as breast-feeding, and infections or immunisations early in life were found to be associated with the incidence of AD.[14] However, whether these environmental factors are related to the development of AD is still controversial.[15]

The objective of this study was to evaluate the risk factors of AD in Korean children (6-7 years) and adolescents (12-13 years) in 2010.

Methods

Study design and subjects

We carried out a cross-sectional survey of 4,003 children aged 6-7 years and 4,112 students aged 12-13 years, chosen from a random sample of 45 elementary and 40 middle schools across the nation. The sampling frame was based on a comprehensive national list of schools in Korea. The participants of this survey were selected using a stratified two-stage cluster sampling design.[16] For the first stage of sampling, schools were stratified by geographic regions and the type of school location (metropolitan cities, urban areas, rural areas). From each stratum, sample schools were selected using the systematic probability proportional to size sampling procedure. The measure of size was the number of classes in the school. Before sample selection, the school frame was ordered by region, zip code, and school enrolment. The participation rates of originally sampled schools were 82% and 80% for elementary and middle schools, respectively. The nonparticipating schools were substituted with "replacement schools" to meet the predetermined sample size. For the second stage of sampling, three classes were selected randomly within each sample school and all children in the sample classes were asked to take part in the survey. Parents were asked to complete questionnaires describing basic demographic information, including age, sex, region, urbanisation, and monthly income of the family. The survey was conducted between September and November 2010. This survey period was the same as in our previous surveys in 1995 and 2000.[10] School locations were classified into 3 groups, i.e. metropolitan, urban, and rural areas. The metropolitan areas contained more than one million people. Among the areas with population sizes of less than one million, urban and rural areas were divided by the population density of 300 persons/km^2. The response rates of the 6-7 year-old and 12-13 year-old children were 92.1% and 93.8%, respectively.

This study was approved by the institutional review board (IRB) at Dankook University in Cheonan (IRB approval number: DKUH IRB 2010-09-0260). Written informed consent was confirmed by the IRB and obtained from all parents prior to participation in this study.

Assessment of risk factors by questionnaire

In this study, a Korean version of the ISAAC questionnaire was used. Detailed characteristics of our questionnaire have been previously reported.[10] The prevalence of the following cases were determined: 1) those who have experienced itchy eczema episodes in their lifetime; 2) those who have experienced itchy eczema episodes within 12 months of the survey; 3) those who have been diagnosed with AD by a physician in their lifetime; and 4) those who have received treatment for AD within 12 months of the survey. Additional questions were included in the core questionnaire to investigate the basic socio-demographic information,

including age, sex, residential area and monthly income of family, and potential risk factors which might influence the development or exacerbation of AD among these schoolchildren. For the elementary school students, parents were asked to complete the questionnaires, whereas middle school students themselves answered the questions on the prevalence of allergic diseases.

Skin prick tests

The following 18 inhalant allergens were selected for the standard skin prick test (SPT) panel: *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f), *Tyrophagus putrescentiae* (Tyr p), cockroach, cat, dog, alder, birch, oak, Japanese cedar, orchard grass, Bermuda grass, timothy, mugwort, ragweed, Japanese hop, Alternaria, and *Aspergillus fumigates*. The allergens were provided by Allergopharma, Reinbek, Germany, except for Japanese cedar (Lofarma, Milan, Italy). Histamine was used as a positive control and normal saline as a negative control. Fifteen minutes after the SPT, the largest diameter of the wheal and its perpendicular diameter for each allergen were measured. Both diameters were recorded, summed, and divided by two. For the present study, atopy was taken to be synonymous with allergic sensitisation, with the latter being understood as representing positivity to at least one allergen, and a wheal 3 mm or greater than wheal size of positive control.

Statistical analysis

Because the participants for this survey were selected using a stratified two-stage cluster sampling design, we constructed the sampling weights for this study to take into account differential selection probabilities, non-response and post-stratification. SAS version 9.1 (SAS Institute, Cary, NC) was used for statistical analyses. The prevalence rates of AD by sex, age, and region were calculated and compared using the chi-square test (when necessary, Fisher's exact test was used) and 95% confidence intervals (CIs) using the SURVEYFREQ Procedure. Logistic regression analysis was used to assess the association with polychotomic variables – defining which factors are correlated to AD (assigning risk factors) using the SURVEYLOGISTIC Procedure. Statistical significance of associations was accepted for $p<0.05$. We adjusted age, sex, and atopy as personal factors, parental allergic disease as the familial factor, and living area, remodelling and moving house as environmental factors in the multivariate analysis.

Results

A total of 4,003 children aged 6-7 years and 4,112 of adolescents aged 12-13 years participated in this study. The demographic and geographical characteristics of the study population are demonstrated in Table 1. The study subjects included 2,021 (50.5%) boys aged 6-7 years (children) and 2,029 (49.3%) boys aged 12-13 years (adolescents).

Table 1. Characteristics of the study population

	6-7 years old (N=4,003)	12-13 years old (N=4,112)
Sex (Male/Female)	2021/1982	2029/2083
Family history of atopic dermatitis		
father	220/3482 (6.3%)	130/3453 (3.8%)
mother	208/3537 (5.9%)	147/3553 (4.1%)
sibling	950/3285 (28.9%)	900/3485 (25.8%)
Residential area		
Metropolitan	1863 (46.5%)	1824 (44.4%)
Urban area	1461 (36.5%)	1665 (40.5%)
Rural area	679 (17.0%)	623 (15.2%)
Economic state (monthly income)		
< 1,990,000 KRW	546 (14.1%)	616 (15.7%)
2,000,000-4,000,000 KRW	1939 (49.9%)	1689 (43.2%)
4,000,001-6,000,000 KRW	982 (25.3%)	1,074 (27.4%)
> 6,000,000 KRW	418 (10.8%)	534 (13.65)
Prevalence of AD		
Itchy eczema, ever	1080 (27.0%)	806 (19.9%)
Itchy eczema, last 12 months	824 (20.6%)	531 (13.1%)
AD diagnosis, ever	1424 (35.6%)	981 (24.2%)
AD treatment, last 12 months	612 (15.3%)	361 (8.9%)
Sensitization to inhalant allergens	371/899 (41.3%)	369/613 (60.2%)*

KRW; Korean won (the currency of the Republic Korea), AD; Atopic Dermatitis

*$P < 0.05$

Table 2. Risk factor analysis for atopic dermatitis in 6-7 year old children

	N(%)	OR (95% CI)	aOR (95% CI)
Sex (female)	702/1,976 (35.5)	0.99 (0.87-1.13)	
Atopy	670/1,608 (41.7)	1.55 (1.36-1.77)*	1.53 (1.32-1.82)†
Maternal allergy	652/1,482 (44.0)	1.78 (1.55-2.03)*	1.76 (1.51-2.08)†
Paternal allergy	562/1,283 (43.8)	1.68 (1.46-1.92)*	1.68 (1.42-1.97)†
Breast milk feeding	1,060/2,954 (35.9)	1.03 (0.88-1.19)	
Cesarean section	526/1,503 (35.0)	0.96 (0.84-1.10)	
Antibiotics use during infancy	607/1,419 (42.8)	1.22 (1.12-1.46) *	1.09 (0.88-1.39)
Household pets during infancy	94/239 (39.3)	1.19 (0.91-1.55)	
Exposure to smoking during pregnancy	5/23 (21.7)	0.52 (0.19-1.41)	
Moving into a newly built house during infancy	301/714 (42.2)	1.40 (1.19-1.65)*	1.35 (1.13-1.63)†
Income (< $2,000/month)	178/545 (32.7)	0.86 (0.71-1.05)	
Residential area (Urban)	1,206/3,314 (36.4)	1.14 (0.99-1.32)	
Exposure to smoking (at present)	822/2,312 (35.6)	0.98 (0.86-1.12)	
Household pets (at present)	118/346 (34.1)	0.93 (0.74-1.18)	
House located near the pollutant area	368/987 (37.3)	1.10 (0.95-1.28)	
Visible mold in the house (at present)	413/1,057 (39.1)	1.24 (1.16-1.42)*	1.15 (1.04-1.37)†
Living in the apartment (at present)	942/2,630 (35.8)	1.06 (0.92-1.23)	
Remodelling within 12 months	244/617 (39.5)	1.21 (1.02-1.45)*	1.14 (0.91-1.46)

* p <0.01, † p <0.05

Logistic regression analysis was used and all the risk factors were adjusted by age, sex, and atopy, presence of parental allergic disease, living area, remodeling and moving into a newly built house in multivariate analysis.

In children aged 6-7 years, the prevalence of 'itchy eczema, ever' was 27.0% and the prevalence of 'itchy eczema, lasting for 12 months' was 20.6%. The lifetime prevalence of AD diagnosis was 35.6% and the prevalence of AD treatment in the last 12 months was 15.3%. On the other hand, in the 12 to 13 year age group, the prevalence of 'itchy eczema, ever' and 'itchy eczema, lasting for 12 months' was 19.9% and 13.1%, respectively. The lifetime prevalence of AD diagnosis was 24.2% and the prevalence of AD treatment in the last 12 month was 8.9%.

In children who have ever been diagnosed with AD, comorbidity with 'asthma diagnosis, ever' was found in 14.9% and 12.9% in 6-7 year-old and 12-13 year-old children, respectively. Among the 'AD diagnosis, ever' groups, 'allergic rhinitis diagnosis, ever' was 47.6% in 6-7 year old children and 46.8% in 12-13 year-old adolescents.

Sensitisation rate to common inhalant allergens was higher in the 12-13 year-old group than in the 6-7 year-old group with AD (60.2% vs. 41.3%, P=0.011). Sensitisation to *Der p* was found to be the most prevalent in 6-7 year-old AD children (38.7%), followed by *Der f* (37.9%), Japanese hop (6.6%), *Tyr p* (5.9%), oak (5.9%), birch (5.1%), and alternaria (4.3%). In 12-13 year-old adolescents with AD, *Der p* also showed the highest prevalence (47.7%), followed by *Der f* (46.5%), Japanese hop (12.7%), *Tyr p* (11.6%), oak (11.4%), cat (11.3%), and Alternaria (8.8%).

In the univariate logistic regression analyses for 'AD diagnosis, ever', seven variables reached statistical significance in 6-7 year-olds (Table 2). Possible risk factors for AD in 6-7 year-old schoolchildren were atopy, a parental history of allergic disease, the usage of antibiotics during infancy, a history of having moved into a newly built house during infancy, the presence of visible

mould in the house, and remodelling of house within 12 months.

Although the adjusted odd ratios (aOR) were slightly lower in the multivariate logistic regression than in the univariate analysis, the statistical significance persisted after adjustment in atopy (aOR 1.53, 95% CI 1.32-1.82), the presence of parental allergic diseases (maternal allergy aOR 1.76, 95% CI 1.51-2.08; paternal allergy aOR 1.68, 95% CI 1.42-1.97), moving into a newly built house during infancy (aOR 1.35, 95% CI 1.13-1.63) and visible mould in the house (aOR 1.15, 95% CI 1.04-1.37). However, antibiotic use during infancy and remodelling within 12 months showed no statistical significance as a risk factor for AD.

In the univariate logistic regression analyses for 'AD diagnosis, ever' in 12-13 year-old schoolchildren, nine variables were shown to be possible risk factors. They were female sex, atopy, a parental history of allergic diseases, antibiotic use during infancy, living in the house located near the pollutant area, the presence of visible mould in the house, living the in apartment and a history of having moved into a newly built house during infancy. Multivariate logistic regression analysis demonstrated that female sex (aOR 1.25, 95% CI 1.01-1.69), atopy (aOR 1.60, 95% CI 1.31-2.01), a parental history of allergic diseases (maternal allergy aOR 2.12, 95% CI 1.75-2.63; paternal allergy aOR 1.98, 95% CI 1.60-2.48), the presence of visible mould in the house (aOR 1.43, 95% CI 1.09-1.93), and a history of having moved into a newly built house during infancy (aOR 1.53, 95% CI 1.05-2.29) were associated with AD, while statistical significance disappeared after adjusting with confounding factors in antibiotic use during infancy, living in the house near the pollutant area and living in the apartment.

We did not find any relation between AD and other risk factors including breast milk feeding, the

Table 3. Risk factor analysis for atopic dermatitis in 12-13 year old children

	N (%)	OR (95% CI)	aOR (95% CI)
Sex (female)	522/2,045 (25.5)	1.40 (1.30-1.54)*	1.25 (1.01-1.69)†
Atopy	591/2,164 (27.3)	1.46 (1.26-1.70)*	1.60 (1.31-2.01)†
Maternal allergy	348/1,016 (34.3)	1.98 (1.70-2.32)*	2.12 (1.75-2.63)†
Paternal allergy	273/807 (33.8)	1.84 (1.55-2.17)*	1.98 (1.60-2.48)†
Breast milk feeding	636/2,593 (24.5)	1.04 (0.89-1.22)	
Cesarean section	355/1,522 (23.3)	0.91 (0.79-1.06)	
Antibiotics use during infancy	288/914 (31.5)	1.21 (1.06-1.60)*	1.04 (0.86-1.34)
Household pets during infancy	45/206 (21.8)	0.86 (0.61-1.20)	
Exposure to smoking during pregnancy	3/16 (18.8)	0.77 (0.22-2.71)	
Moving into a newly built house during infancy	169/609 (27.8)	1.24 (1.02-1.51)*	1.53 (1.05-2.29)†
Income (< $2,000/month)	113/601 (18.8)	0.68 (0.54-0.84)	
Residential are (Urban)	832/3,436 (24.2)	1.01 (0.83-1.24)	
Exposure to smoking (at present)	616/2,464 (25.0)	1.11 (0.96-1.29)	
Household pets (at present)	156/642 (24.3)	0.99 (0.81-1.21)	
House located near the pollutant area	282/1,036 (27.2)	1.24 (1.06-1.46)*	1.07 (0.79-1.62)
Visible mold in the house (at present)	150/989 (15.2)	1.21 (1.03-1.43)*	1.43 (1.09-1.93)†
Living in the apartment (at present)	651/2,544 (25.6)	1.29 (1.10-1.52)*	1.22 (0.99-1.53)
Remodelling within 12 months	169/668 (25.3)	1.07 (0.88-1.29)	

*p <0.01, †p <0.05

Logistic regression analysis was used and all the risk factors were adjusted by age, sex, and atopy, presence of parental allergic disease, living area, remodeling and moving into a newly built house in multivariate analysis.

age at introduction of solid food, delivery type at birth, the exposure to any pets in the past or present, passive smoking, socioeconomic status estimated by monthly income, residential area, living near the pollutant area, house remodelling or living in apartment.

Discussion

Sensitisation to inhalant allergens was more frequently found in 12-13 year-old children with AD than in 6-7 year olds. Although the presence of sensitisation to food allergens was not evaluated in this study, our finding is consistent with the previous study.[17] Sensitisation rate to inhalant allergens is higher in children with AD than in general population,[16] indicating that atopy is associated with AD. We also found that 14.9% of 6-7 year-old and 12.9% of 12-13 year-old children with AD had asthma, and 40-50% of AD children had ever been diagnosed with allergic rhinitis. Because AD might be an 'entry point' for the subsequent development of asthma or allergic rhinitis, children with AD need proper management to prevent epicutaneous sensitisation leading to systemic immune response.[18]

In our study, sex did not significantly influence AD in 6-7-year-old children, but there was a high prevalence of AD in female 12-13 year-old schoolchildren. Our result is in agreement with a Spanish study where a greater prevalence of rhinitis and AD in females was observed in 13 and 14 year-old adolescents.[19] This suggests the implication of hormonal factors on the presence of allergic disorders. However, gender difference in AD development is controversial, as the prevalence of asthma and rhinitis symptoms was greater in males, but no difference for eczema was observed in 3,000 British pre-pubertal children.[20]

We found a history of having moved into a newly built house during infancy as a risk factor for AD, which is in agreement with the results of Lee et al.[21] A recent study in Japan identified chemical substances emitted from indoor building materials, such as formaldehyde and volatile organic compounds as major causes of sick building syndrome;[22] these chemicals may increase the risk of allergic disease.[23] A prospective birth cohort study demonstrated that redecoration activities such as painting, floor covering and new furniture before birth and in the first year of life increased the risk of developing eczema.[24] However, the mechanism is not clear and further studies are needed.

Parental history of allergic diseases constitutes a risk factor for childhood AD in the present study as in the previous study.[25] The greater risk in children with maternal than with paternal allergic diseases could be due to the fact that it is generally the mothers who complete the questionnaires in 6 and 7 year-old schoolchildren. Another possible explanation is that oestrogen from mothers is a proinflammatory hormone, whereas male steroids from fathers act as the immune suppressors.[26] One more interesting notion in our study is that adjusted odds ratio of parental allergic diseases was higher in 12-13 year-old children than 6-7 year-old children whose AD symptoms developed mostly during the first 5 years of life. This result suggests that the development of AD in infants or young children might be affected by genetic factors less significantly than in older children. Probably, environmental factors such as exposure to various chemical irritants in a newly built house during infancy might have an important role in the development of AD in young age group.

We found a statistically significant association between mould in the house and the presence of AD in both age groups. A Spanish study demonstrated that exposure to certain home conditions related to moulds in the first year of life increased the risk of allergic disease, but having good isolating windows in the first year of life protected against severe atopic eczema.[27] Unfortunately, the authors did not show the exact level of exposure to fungi and finally failed to provide direct causal relationship. In our study, we assessed visible mould in the house at the time of survey, not during infancy. Unless the children participating in this study have lived in the same house, mould exposure might not be involved in the development of AD. Therefore, in 6-7 year-old children, mould in the house seems more likely to act as an aggravating factor in pre-existing AD rather than a causative factor. In contrast, in 12-13 year-olds, exposure to mould in the house showed higher odds ratio than in 6-7 year-olds. In this older age group, mould might cause AD or be a surrogate of other risk factors responsible for the development of AD.

We could not find any association of AD with either breast milk feeding or the age at introduction of solid foods (data not shown). In a birth cohort study of Holland, breast milk feeding from mothers who do not have any allergic disease prevents the development of AD.[28] However, recent studies failed to confirm the 'conventional wisdom' that

breastfeeding is protective against allergy and asthma.[29] Some authors consider the introduction of solid food before the age of 4 months to constitute a greater risk of AD at the ages of 2, 3 and 10 years.[30] There is still controversy, however, and our study did not show any supportive data on feeding-related risk factors in association with AD development.

This study was a nationwide population-based survey to analyse the risk factors of AD in elementary and middle school children in Korea. Using a stratified, two-stage cluster-sampling design, we estimated representative prevalence from a large sample size of two age groups across the nation, and selected children with AD for risk factor analysis. It means that our results can be generalised in the Korean situation. Nevertheless, several limitations must be taken into account. Our study design was a cross-sectional survey which cannot identify the causal relationship. In addition, the diagnosis of AD was based on a questionnaire, not by detailed history and physical examination.

In conclusion, risk factors such as atopy, the presence of parental allergic diseases, moving into a newly built house during infancy and visible mould in the house were associated with AD in Korean schoolchildren. Further investigation by prospective cohort study is required to prove the causal relationship between the development of AD and risk factors in Korean children.

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