

Interaction between *IL13* genotype and environmental factors in the risk for allergic rhinitis in Korean children

Woo Kyung Kim, MD, PhD,^{a,b,*} Ji-Won Kwon, MD,^{c,*} Ju-Hee Seo, MD,^d Hyung Young Kim, MD,^d Jinho Yu, MD, PhD,^d Byoung-Ju Kim, MD, PhD,^e Hyo-Bin Kim, MD, PhD,^f So Yeon Lee, MD, PhD,^g Kyung Won Kim, MD, PhD,^h Mi-Jin Kang, BS,ⁱ Yee-Jin Shin, MD, PhD,^j and Soo-Jong Hong, MD, PhD^d *Seoul, Korea*

Background: The prevalence of allergic rhinitis (AR) is increasing worldwide. Allergic diseases develop in susceptible subjects when they are exposed to specific environmental factors.

Objective: We analyzed changes in the prevalence of AR and identified genetic and environmental factors in early childhood that affect risk.

Methods: We used the International Study of Asthma and Allergies in Childhood questionnaire to collect data on AR, allergies, and environmental exposures from 4554 elementary school students from 5 areas of Seoul, Korea, in 2008. We also obtained DNA from 1050 subjects from 1 area of Seoul for genotype analysis of *IL13*.

Results: We identified genetic and environmental factors during infancy and early childhood that increased the risk for current AR (resulting in a diagnosis of AR and AR symptoms in the past 12 months) in elementary school-aged children. These included allergic disease in parents and antibiotic use in infants, allergic disease in parents and exposure of infants to mold, and allergic disease in parents and moving an infant to a newly built house. The risk of current AR also increased in subjects with GA or AA at nucleotide 2044 in *IL13* who had been exposed to mold in the home during infancy (adjusted odds ratio, 3.27; 95% CI, 1.75-6.11) compared with subjects who had GG at this position and had not been exposed to mold (adjusted odds ratio, 3.27; 95% CI, 1.75-6.11).

Conclusion: The prevalence of AR is increasing in Korean children. Children with a family history of allergic disease and exposure to specific environmental risk factors during infancy

are more likely to have AR. Children with GA or AA at *IL13*(+2044) are at increased risk for AR when exposed to mold in the home during the first year of life. (*J Allergy Clin Immunol* 2012;130:421-6.)

Key words: Allergic rhinitis, prevalence, risk factor, *IL-13* polymorphism, gene-environment interaction, infancy

The International Study of Asthma and Allergies in Childhood (ISAAC) was the first worldwide study of childhood asthma performed with standardized questionnaires; it resulted in a global map of disease prevalence.^{1,2} The study showed that the prevalence of childhood allergic rhinitis (AR) varies worldwide, ranging from 0.8% to 39.7%.³

There are many risk factors for AR, which vary with stage of life. Potential risk factors identified by using epidemiologic studies include family history of atopy, birth month, parental smoking, male sex, and early exposure to allergens or pollutants.¹⁻⁴ Other studies identified frequent respiratory tract infections, administration of antibiotics, or a cat in the home in the first year of life; dampness in the home; perianal redness; and dietary habits as risk factors.⁵ Despite the extensive list of risk factors, it is still not clear which are the major determinants for development of AR.^{1-4,6}

Little is known about how genetic and environmental factors or their interactions contribute to the development and progression of AR.⁷ During infancy and childhood, environmental factors could alter epigenetic mechanisms of disease development; researchers have also analyzed the effects of interactions between genetic polymorphisms and environmental factors on the development of asthma and atopy.⁸⁻¹¹

The polymorphism *CD14*-159C/T affects sensitivity to allergies and eczema, depending on the extent of endotoxin exposure.¹² Similarly, the effect of this polymorphism on the development of nasal allergy and atopy varies with exposure to farms during childhood.¹³ The polymorphism *CD14*-172A/G interacts with consumption of farm milk to affect the risk for asthma and symptoms of allergic rhinoconjunctivitis.¹⁴

IL-13+2044G/A (rs20541) is a single nucleotide polymorphism (SNP) in the coding region of this gene; expression of this *IL13* variant was associated with asthma,^{15,16} atopy,¹⁷ and increased total serum IgE levels in a birth cohort. Previous studies of *IL13* polymorphisms and AR reported that SNPs in *GATA3* (rs105820) and *IL13* (rs1800925) interacted to affect the risk for AR¹⁸; this same *IL13* polymorphism was associated with the development of AR in our study of a Korean population.¹⁹ We investigated whether the *IL13*+2044G/A polymorphism interacts with environmental factors to affect the risk for AR.

Little is known about the epidemiology of AR. Rhinitis symptoms occur occasionally in healthy subjects, and there are few standardized and validated methods for identifying rhinitis,

From ^athe Department of Pediatrics and ^bthe Allergy and Respiratory Research Laboratory, Inje University Seoul Paik Hospital; ^cthe Department of Pediatrics, Seoul National University Bundang Hospital; ^dthe Department of Pediatrics, Childhood Asthma Atopy Center, Asan Medical Center, Research Center for Standardization of Allergic Diseases, University of Ulsan College of Medicine; ^ethe Department of Pediatrics, Inje University Haeundae Paik Hospital; ^fthe Department of Pediatrics, Inje University Sanggye Paik Hospital; ^gthe Department of Pediatrics, Hallym University Sacred Heart Hospital; ^hthe Department of Pediatrics, Severance Children's Hospital, College of Medicine, Yonsei University; ⁱthe Asan Institute for Life Science; and ^jthe Department of Psychiatry, Severance Hospital, College of Medicine, Yonsei University.

*These authors contributed equally to this work.

Supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health and Welfare, Republic of Korea (A092076).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 11, 2011; revised April 19, 2012; accepted for publication April 23, 2012.

Corresponding author: Soo-Jong Hong, MD, PhD, Department of Pediatrics, Childhood Asthma Atopy Center, Research Center for Standardization of Allergic Diseases, Asan Medical Center, University of Ulsan College of Medicine, Pungnap 2-dong, Songpa-gu, Seoul 138-736, Korea. E-mail: sjhong@amc.seoul.kr.

0091-6749/\$36.00

© 2012 American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2012.04.022

Abbreviations used

aOR: Adjusted odd ratio
 AR: Allergic rhinitis
 ISAAC: International Study of Asthma and Allergies in Childhood
 OR: Odds ratio
 SNP: Single nucleotide polymorphism

which might account for the scarcity of epidemiologic data. We conducted this study as a part of the Seoul project Atopy-Free Seoul. We aimed to identify changes in the prevalence of AR in elementary school children in Seoul, Korea, from 1995 to 2008^{6,20,21}; risk factors for AR; and the effect of genetic and environmental factors on the development of AR.

METHODS**Study subjects**

We recruited 5036 students in first to sixth grades from 5 elementary schools randomly selected from 5 areas of Seoul (downtown, northeastern, northwestern, southeastern, and southwestern areas). Students received a physical examination, and parents of 4731 students responded to a questionnaire (response rate, 93.9%). Data were analyzed from 4554 students whose parents answered at least the basic questions (about students' age and sex; $n = 2317$, 50.9% boys). DNA samples from 1050 students who resided in 1 area of Seoul were processed for *IL13* (rs20541) genotype analysis.

Questionnaire

In 2008, parents or guardians of the children included in the study all completed a modified form of the ISAAC questionnaire. Results were compared with those from administration of the same questionnaire to the same schools in 1995, 2000, and 2005. The questionnaire included sections about students' (1) general characteristics, including name, sex, date of birth, height, and weight; (2) history of symptoms related to AR; and (3) exposure to environmental factors associated with allergic diseases. Written consent was obtained from all parents or guardians; the study was approved by the Institutional Review Board of Asan Medical Center, Ulsan University, Seoul, Korea.

Prevalence of AR

We determined the prevalence of (1) sneezing or runny or blocked nose at any point in a lifetime (ie, AR symptoms ever), (2) sneezing or runny or blocked nose and AR symptoms within 12 months of survey completion (ie, AR symptoms in the last 12 months), (3) a diagnosis of AR at any point in a lifetime (ie, AR diagnosis ever), and (4) treatment for AR within 12 months of survey completion (ie, AR treatment in the last 12 months). Prevalence values were compared based on age, sex, and geographic area. Current AR was defined as having received a diagnosis of AR at any point in a lifetime and having AR symptoms within 12 months of survey completion.

Genotype analysis

Genomic DNA was prepared from peripheral blood samples by using a G-DEX II kit (Intron, Seoul, Korea). The *IL13* +2044G/A polymorphism was detected by means of PCR RFLP analysis. In brief, a 210-bp DNA fragment, including the polymorphic site, was amplified by using the primers 5'-CTT CCG TGA GGA CTG AAT GAG ACG GTC-3' and 5'-GCA AAT AAT GAT GCT TTC GAA GTT TCA GTG GA-3'. The restriction enzyme for RFLP was *NlaIV* (New England BioLabs, Beverly, Mass), which cleaves the G allele to generate fragments of 178 and 32 bp in size. We randomly selected 20% of the subjects for DNA sequence analysis of this polymorphism and confirmed the accuracy of our results.

Statistical analysis

Data were compared based on children's sex, age, school grade, and geographic area using χ^2 analysis. In the risk factor analysis odds ratios (ORs) and 95% CIs were obtained by using logistic regression. All statistical analyses were performed with SPSS software 14.0 (SPSS, Chicago, Ill). A P value of less than .05 was considered statistically significant. Interactions were investigated between parental history of allergic disease, exposure to specific environmental factors during infancy (use of antibiotics for >3 days, mold in the house, or moving into a newly built house), and current AR. Data from subjects were divided into 4 groups based on exposure to mold and *IL13* genotype, and logistic regression was used to estimate aORs for age, sex, and family history of AR. We also evaluated ORs in additive and multiplicative models by using interaction terms.

RESULTS**Characteristics of study participants**

We analyzed data from 2317 boys and 2237 girls (mean age, 9.50 ± 1.73 years). A history of asthma and AR were reported for 3.1% and 31.8% of the parents, respectively. Exposure to secondhand smoke was recorded for 38.7% of the children (Table I).

AR prevalence in Seoul in 1995, 2000, 2005, and 2008

The lifetime prevalence of AR symptoms ever fluctuated only slightly, from 39.6% in 1995 to 37.2% in 2000, 39.6% in 2005, and 39.4% in 2008. The prevalence of AR symptoms in the 12 months before survey completion decreased from 33.4% in 1995 to 31.4% in 2000, but it increased again to 35.1% in 2005 and 35.8% in 2008. By contrast, the lifetime prevalence of AR diagnosis increased throughout the study period, from 16.8% in 1995 to 22.0% in 2000, 26.4% in 2005, and 34.1% in 2008. The prevalence of AR treatment in the 12 months before survey completion showed the same trend, increasing from 12.7% in 1995 to 15.8% in 2000, 19.4% in 2005, and 26.1% in 2008. The prevalence of current AR also increased, from 11.9% in 1995 to 14.2% in 2000, 19.4% in 2005, and 22.2% in 2008 (Table II).^{6,20,21} In the test for linearity over time, positive correlations were found in the prevalence of AR diagnosis ever, AR treatment in the last 12 months, and current AR (P for linearity = .027, .045, and .014, respectively). However, there was no significant trend in the prevalence of AR symptoms ever and in the last 12 months (P for linearity = .821 and .301, respectively).

Risk factors for current AR

The independent risk factors for current AR were male sex (adjusted odds ratio [aOR], 1.38; 95% CI, 1.14-1.67), history of atopic dermatitis (aOR, 2.08; 95% CI, 1.71-2.52), history of asthma (aOR, 3.09; 95% CI, 2.29-4.16), parental history of allergic disease (aOR, 3.44; 95% CI, 2.86-4.15), and higher maternal level of education (aOR, 1.33; 95% CI, 1.08-1.63). We also identified a number of environmental factors that were independent risk factors for AR, including the use of antibiotics for more than 3 days during infancy (aOR, 1.95; 95% CI, 1.61-2.36), a history of bronchiolitis before 2 years of age (aOR, 1.94; 95% CI, 1.50-2.50), exposure to molds in the home during infancy (aOR, 1.83; 95% CI, 1.37-2.44), and exposure to molds in the home within 12 months of survey completion (aOR, 1.37; 95%

TABLE I. Subjects' characteristics

Characteristic	Mean $\pm$ SD or proportion	No. of respondents
Age (y), mean $\pm$ SD	9.50 $\pm$ 1.73	4554
Sex (M/F)	2317/2237	4554
BMI (kg/m ²), mean $\pm$ SD	17.91 $\pm$ 3.14	3710
Maternal educational degree ($>$ high school)	2690 (60.8%)	4423
Economic status (monthly income)		
Low ($\leq$ 1999 USD)	554 (12.6%)	4382
Middle (2000-4999 USD)	3209 (73.2%)	
High ($\geq$ 5000 USD)	619 (14.1%)	
Parental history of allergic diseases (asthma, AR, or AD)	1458 (37.6%)	3882
Parental history of asthma	125 (3.1%)	4025
Parental history of AR	1279 (31.8%)	4025
Environmental tobacco smoking	1721 (38.7%)	4442
School area		
Downtown	734 (16.1%)	4554
Northeastern	794 (17.4%)	
Northwestern	1023 (22.5%)	
Southeastern	1242 (27.3%)	
Southwestern	761 (16.7%)	

AD, Atopic dermatitis; BMI, body mass index; F, female; M, male; USD, US dollar.

CI, 1.04-1.79; Table III). These findings indicate that early-life environmental factors are associated with development of AR.

Family history of allergic disease and environmental factors during infancy

The subjects were divided into 4 groups based on the presence or absence of a family history of allergic diseases and 1 of the environmental factors to investigate the relationship between genetic and environmental risk factors. The aOR for AR was highest for subjects with more than 3 days of antibiotic use during infancy who had parents with allergic diseases (aOR, 6.00; 95% CI, 4.63-7.80). The aOR for AR was also high among subjects with either of these risk factors (antibiotic use: aOR, 2.24; 95% CI, 1.69-2.97; parents with allergies: aOR, 3.51; 95% CI, 2.74-4.53) compared with subjects without these features (Fig 1, A). The aOR for a parental history of allergic disease and exposure to mold in the home during infancy was 5.95 (95% CI, 4.11-8.61); the aORs for each of these factors were 3.43 (95% CI, 2.80-4.19) and 2.12 (95% CI, 1.40-3.22), respectively (Fig 1, B). The aOR for subjects with a parental history of allergic disease who had moved into a newly built home during infancy was 3.70 (95% CI, 2.55-5.37); the aORs for either of these factors individually were 3.50 (95% CI, 2.86-4.28) and 1.29 (95% CI, 0.87-1.92), respectively (Fig 1, C). A family history of allergic diseases and exposure to environmental risk factors in early life appear to synergize to increase the risk for AR.

IL13+2044 polymorphism and environmental factors during infancy

We also investigated interactions between the IL13+2044 polymorphism and environmental factors in the risk for AR. Overall, none of the SNPs at IL13+2044 increased the risk for AR (aOR, 0.97; 95% CI, 0.71-1.33; see Table E1 in this article's Online Repository at www.jacionline.org). However, the risk for

AR was greater among subjects with GA or AA at IL13+2044 who had been exposed to mold during infancy (aOR, 3.27; 95% CI, 1.75-6.11) than among subjects with the GG genotype who had been exposed to mold during infancy (aOR, 1.14; 95% CI, 0.55-2.37) or those with the GG genotype who had not been exposed to mold as infants (aOR, 1.0; Fig 1, D). There were significant additive ($P = .0002$) and multiplicative ($P = .0144$) interactions after adjusting for age, sex, body mass index, and parental history of AR. The combination of IL13+2044G/A and mold exposure increased the risk for AR with or without atopy (see Table E2 in this article's Online Repository at www.jacionline.org). Genetic factors might therefore interact with early-life mold exposures to increase the risk for AR. There were no interactions between SNPs at IL13+2044 and other environmental factors, such as antibiotic use or moving into a newly built house during infancy, that affected the risk for AR (see Tables E3 and E4 in this article's Online Repository at www.jacionline.org).

DISCUSSION

We observed an increase in AR diagnosis, AR treatment, and current AR among Korean elementary school-aged children from 1995 to 2008 and identified risk factors for current AR. The most important finding from our study was that children with a genetic susceptibility to AR, who were defined as subjects with a parental history of allergic disease or the IL13+2044A allele, were more likely to have AR when they also had a history of exposure to environmental risk factors, particularly during infancy. These findings indicate that specific environmental exposures during early life contribute to the development of AR. We identified specific genetic and early-life environmental factors that interact to increase the risk for AR.

Nearly one third of elementary school students in Seoul had rhinitis, which was defined as sneezing or runny or blocked nose in the absence of a cold or flu. The worldwide ISAAC Phase III study, which was a repetition of the ISAAC Phase I study after a mean of 7 years, revealed an increase in the prevalence of allergic rhinoconjunctivitis that ranged from 2.2% to 45.1%.²² Increases in the prevalence of AR and eczema were reported in Hong Kong from 1995 to 2001.²³ In our study the prevalence of AR diagnosis, AR treatment within 12 months of questionnaire completion, and current AR increased significantly from 1995 to 2008, which was contrary to the prevalence of AR symptoms ever and in the 12 months before the questionnaires were completed. We have no explanation for these discrepancies, but they might result from limitations of the ISAAC questionnaire or increased awareness and accessibility to medical facilities in Korea.

We identified risk factors for AR that included a past history of atopic dermatitis and asthma, family history of allergic diseases, maternal level of education, antibiotic use for more than 3 days in infancy, bronchiolitis before the age of 2 years, and mold exposure in the home or moving to a newly built house during infancy. A family history of allergic disease has been shown to increase children's risk of allergic disease in long-term prospective studies.^{24,25} Our findings support these in that a family history of allergic disease appears to be a risk factor for AR.

Several studies have associated antibiotic use with the development of asthma and AR^{26,27}; antibiotics might alter the intestinal flora and/or prevent bacterial infections to induce an atopic

TABLE II. Prevalence of AR in Korean children (1995-2008)

	1995 ^{6,21} (n = 7963)	2000 ^{6,21} (n = 7971)	2005 ²⁰ (n = 7827)	2008 (n = 4554)	P value for linearity*
AR symptoms, ever	39.6 (38.5-40.7)	37.2 (36.1-38.3)	39.6 (38.5-40.8)	39.4 (37.9-40.9)	.821
AR symptoms, last 12 mo	33.4 (32.3-34.5)	31.4 (30.3-32.4)	35.1 (34.0-36.2)	35.8 (34.4-37.2)	.301
AR diagnosis, ever	16.8 (16.0-17.6)	22.0 (21.1-22.9)	26.4 (25.4-27.3)	34.1 (32.7-35.5)	.027
AR treatment, last 12 mo	12.7 (12.0-13.4)	15.8 (15.0-16.6)	19.4 (18.5-20.3)	26.1 (24.8-27.4)	.045
Current AR†	11.9 (11.2-12.6)	14.2 (13.4-15.0)	19.4 (18.5-20.3)	22.2 (21.0-23.4)	.014

*The P value for linearity was found by evaluating the variation in the prevalence of AR according to each time point with a linear regression model.

†Current AR was defined when children had received a diagnosis of AR in their lifetime and experienced AR symptoms in the last 12 months.

TABLE III. Risk factors for current AR in Korean children

	No.	Univariate analysis			Adjusted analysis*	
		Percent	OR (95% CI)	P value	aOR (95% CI)	P value
Personal characteristics						
Age (continuous variable)	4554		NA	NA	0.98 (0.92-1.04)	.983
Sex (male)	2317/4554	50.9	1.49 (1.29-1.72)	<.001	1.38 (1.14-1.67)	.001
BMI (≥85th percentile)	641/3710	17.3	0.89 (0.71-1.11)	.285	0.90 (0.70-1.16)	.418
Past history of AD diagnosis	1389/4430	31.4	2.37 (2.04-2.74)	<.001	2.08 (1.71-2.52)	<.001
Past history of asthma diagnosis	343/4364	7.9	3.32 (2.63-4.17)	<.001	3.09 (2.29-4.16)	<.001
Genetic factors						
Parental allergic diseases	1458/3882	37.6	3.74 (3.19-4.38)	<.001	3.44 (2.86-4.15)	<.001
Socioeconomic factors						
Paternal education (≥ graduate)	3217/4451	72.3	1.56 (1.31-1.85)	<.001	1.06 (0.79-1.42)	.695
Maternal education (≥ graduate)	2690/4423	60.8	1.50 (1.29-1.75)	<.001	1.33 (1.08-1.63)	.008
Location of school						
Downtown	734/4554	16.1	NA	<.001 (χ ²)	1	NA
Northeastern	794/4554	17.4			1.73 (1.17-2.58)	.006
Northwestern	1023/4554	22.5			1.36 (0.92-2.00)	.116
Southeastern	1242/4554	27.3			1.40 (0.95-2.04)	.082
Southwestern	761/4554	16.7			1.06 (0.67-1.68)	.781
Environmental factors						
Breast milk feeding ≥6 mo	1212/4535	26.7	0.87 (0.73-1.04)	.134	0.85 (0.69-1.06)	.143
Delivery (cesarean section)	1798/4508	39.9	1.22 (1.01-1.47)	.037	1.03 (0.85-1.24)	.795
Environmental tobacco smoke	1721/4442	38.7	0.91 (0.79-1.06)	.246	1.05 (0.86-1.27)	.646
Current pet ownership	373/4518	8.3	0.91 (0.79-1.06)	.246	0.98 (0.69-1.36)	.847
Pet ownership in pregnancy or in infancy	192/4424	4.3	0.80 (0.61-1.05)	.105	0.67 (0.40-1.11)	.120
Having older siblings	2101/4554	46.1	0.77 (0.42-1.41)	.394	0.59 (0.26-1.31)	.193
Having younger siblings	1532/4554	33.6	2.28 (0.96-5.38)	.054	1.87 (0.61-5.73)	.271
Antibiotics (≥3 d in infancy)	1528/4436	34.4	2.52 (2.18-2.92)	<.001	1.95 (1.61-2.36)	<.001
Past history of bronchiolitis <2 y of age	509/4473	11.4	2.47 (2.02-3.01)	<.001	1.94 (1.50-2.50)	<.001
Mold exposure in house during infancy	428/4159	10.3	2.15 (1.74-2.67)	<.001	1.83 (1.37-2.44)	<.001
Mold exposure in house during recent 12 mo	595/4463	14.2	1.71 (1.41-2.08)	<.001	1.37 (1.04-1.79)	.025
Move to a newly built house in infancy	577/4463	12.9	1.29 (1.05-1.58)	.013	1.19 (0.91-1.55)	.216
Move to a newly built house, ever	1841/4489	41.0	1.38 (1.19-1.59)	<.001	1.20 (0.99-1.45)	.059

AD, Atopic dermatitis; BMI, body mass index; NA, not available.

*Adjusted by age, sex, body mass index, environmental tobacco smoke, parental allergic diseases, maternal degree of education, and each school as categorical variables.

phenotype of the immune system.²⁸⁻³⁰ We associated AR with 3 or more days of antibiotic use in infancy, which is consistent with the hygiene hypothesis. The aOR for current AR was significantly higher for subjects with a combination of genetic and environmental risk factors than for those with no or only 1 risk factor.

In a meta-analysis dampness and mold in homes were associated with a variety of respiratory outcomes, including wheezing and asthma.³¹ We also identified exposure to molds during early childhood as a significant risk factor for the development of wheezing in elementary school children. However, early exposure to fungal agents, such as extracellular polysaccharides from *Aspergillus* or *Penicillium* species, might protect against asthma,³² and therefore further investigations are needed into

the effects of molds on the development of asthma. In our study mold exposures at home during infancy and during the 12 months before survey completion were significantly associated with current AR. Interestingly, we observed that exposure to environmental factors during infancy had a more significant influence on the development of AR than exposure later in life. This supports the conclusions from other researchers that early exposure to allergens has a particularly important role in the development of allergic disease.^{33,34}

Allergic disorders are caused by complex interactions between multiple genetic factors; they occur in genetically predisposed subjects after exposure to environmental factors. The exact causes of most allergic diseases, however, are not well understood because of their complex multifactorial nature. Numerous studies

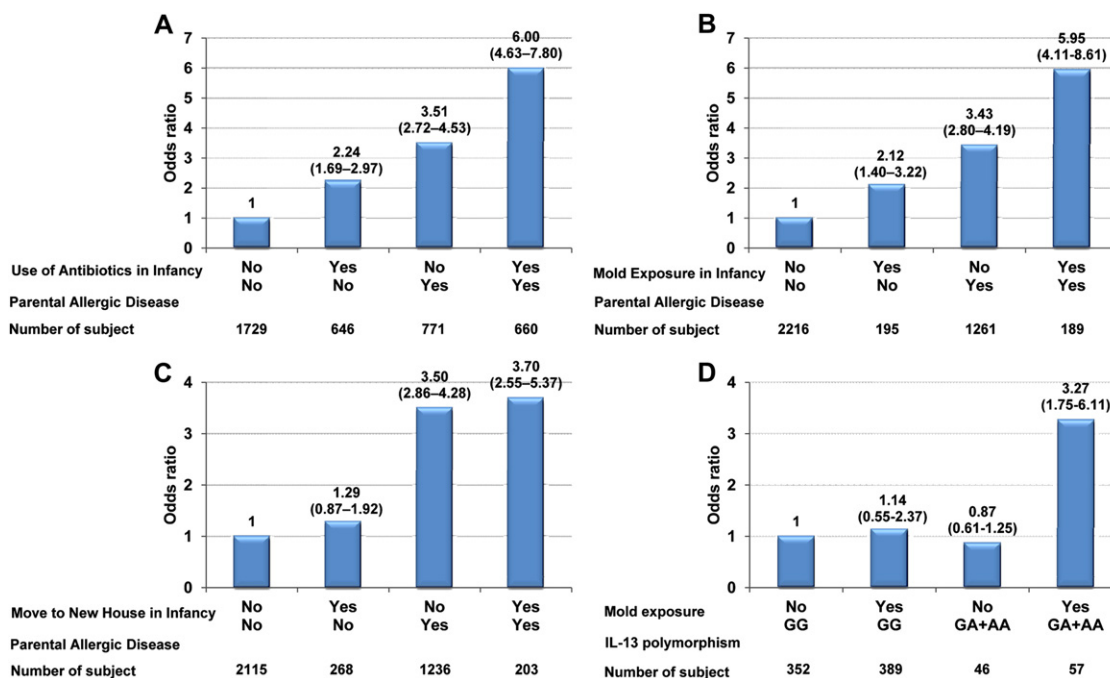


FIG 1. aORs and 95% CIs for AR according to parental history of allergic disease and use of antibiotics in infancy (**A**), mold exposure in infancy (**B**), moving to a newly built house during infancy (**C**), and *IL13*+2044G/A polymorphism and mold exposure during infancy (**D**). Fig 1, A–C, show the highest ORs for current AR in children with a history of environmental factors and parental allergic diseases. Logistic regression analysis adjusted by age, sex, body mass index, environmental tobacco smoking, parental allergic diseases, and maternal level of education was used in each analysis. Fig 1, D, shows the highest ORs for current AR in children who had a history of mold exposure in infancy and the *IL13*+2044G/A polymorphism. There was significant additive ($P = .0002$) and multiplicative ($P = .0144$) interaction after adjusting for age, sex, body mass index, and parental history of AR.

have associated genetic predisposition, urban environment, and Western lifestyle with asthma and allergy.³⁵ Epidemiologic and clinical reports recognized associations between asthma and allergic diseases and exposure to airborne fungi, such as *Alternaria* (in North America) and *Cladosporium* and *Aspergillus* (in Europe) species.³⁶ Despite extensive study, the immunologic mechanisms that mediate the association between fungal exposure and asthma and allergic diseases have not been identified. Airway administration of an extract of the clinically relevant environmental fungus *Alternaria* species induces eosinophilia through innate and adaptive immunity.^{37,38} We associated the SNP *IL13*+2044G/A and mold exposure during the first year of life with the development of AR in Korean children. Although this finding is not consistent with previous results, it appears that the *IL13*+2044G/A polymorphism modifies the effect of mold exposure during the first year of life on the development of AR in Korean children (regardless of atopy status).

There are limitations to our study. The information on environmental exposures was obtained retrospectively and therefore could be affected by recall bias.^{39,40} Furthermore, the prevalence of AR symptoms was calculated based on responses to a questionnaire and therefore could also be affected by recall bias. This is primarily a concern for responses about AR symptoms ever but less so for responses about AR symptoms in the 12 months before survey completion, the major focus of this and the ISAAC study. Our study was also cross-sectional in design, which limited our ability to make conclusions about cause-and-effect relationships between risk factors and disease; prospective studies are

warranted. The number of subjects with the GA+AA genotype and exposure to mold during infancy was small in our study. Studies with larger numbers of subjects are needed to verify this interaction.

Finally, our study might suffer from selection bias because of missing data. To clarify which data are missing, we added a table that compares the characteristics of subjects with complete data and those with missing data (see Table E5 in this article's Online Repository at www.jacionline.org). Because there were some differences between these groups, careful interpretation is needed.

However, our study also has many strengths. The ISAAC questionnaire has been validated in a number of Korean studies, and the analysis of risk factors has been conducted in several previous studies.^{20,21} Our study had a relatively large sample size and a high response rate; it comprised randomly selected children from the first through sixth grades throughout Seoul. The surveys were performed every 5 years at the same schools by the same researchers to investigate the change in prevalence of allergic diseases. Further prospective cohort studies of large numbers of subjects are required to identify further gene-environment interactions associated with AR.

In conclusion, the prevalence of AR in elementary school children in Seoul, Korea, increased from 1995 to 2008. Exposures during infancy to environmental factors, such as antibiotics, mold, or a newly built house, are risk factors for AR. The polymorphism *IL13*+2044G/A appears to interact with mold exposure during infancy to increase the risk for AR. These findings indicate that early-life exposures in genetically susceptible

subjects affect the development of AR. Minimizing exposure to possible environmental risk factors in susceptible infants could reduce the prevalence of AR.

We thank the study participants; their parents and schoolteachers; all joint research workers; the ISAAC epidemiologic survey committee of the Korean Academy of Pediatric Allergy and Respiratory Disease; and In Guk Kim, director of the Songpa-gu Community Health Center, for his assistance with school recruitment.

Clinical implications: *IL13* genotype, parental allergies, and exposure to environmental agents, such as mold, during infancy interact to affect the risk of AR in elementary school-aged children.

REFERENCES

- Montefort S, Ellul P, Montefort M, Caruana S, Agius Muscat H. Increasing prevalence of asthma, allergic rhinitis but not eczema in 5- to 8-yr-old Maltese children (ISAAC). *Pediatr Allergy Immunol* 2009;20:67-71.
- Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997;8:161-76.
- Sly RM. Changing prevalence of allergic rhinitis and asthma. *Ann Allergy Asthma Immunol* 1999;82:233-48.
- Monteil MA, Joseph G, Chang Kit C, Wheeler G, Antoine RM. Smoking at home is strongly associated with symptoms of asthma and rhinitis in children of primary school age in Trinidad and Tobago. *Rev Panam Salud Publica* 2004;16:193-8.
- Tamay Z, Akcay A, Ones U, Guler N, Kilic G, Zencir M. Prevalence and risk factors for allergic rhinitis in primary school children. *Int J Pediatr Otorhinolaryngol* 2007;71:463-71.
- Lee SI. Prevalence of childhood asthma in Korea: international study of asthma and allergies in childhood. *Allergy Asthma Immunol Res* 2010;2:61-4.
- de Marco R, Accordini S, Antonicelli L, Bellia V, Bettin MD, Bombieri C, et al. The Gene-Environment Interactions in Respiratory Diseases (GEIRD) Project. *Int Arch Allergy Immunol* 2010;152:255-63.
- Le Souef PN. Variations in genetic influences on the development of asthma throughout childhood, adolescence and early adult life. *Curr Opin Allergy Clin Immunol* 2006;6:317-22.
- Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery. *Genes Immun* 2006;7:95-100.
- O'Donnell AR, Toelle BG, Marks GB, Hayden CM, Laing IA, Peat JK, et al. Age-specific relationship between CD14 and atopy in a cohort assessed from age 8 to 25 years. *Am J Respir Crit Care Med* 2004;169:615-22.
- Zhang G, Khoo SK, Laatikainen T, Pekkarinen P, Vartiainen E, von Hertzen L, et al. Opposite gene by environment interactions in Karelia for CD14 and CC16 single nucleotide polymorphisms and allergy. *Allergy* 2009;64:1333-41.
- Vercelli D. Discovering susceptibility genes for asthma and allergy. *Nat Rev Immunol* 2008;8:169-82.
- Leynaert B, Guilleud-Bataille M, Soussan D, Benessiano J, Guenegou A, Pin I, et al. Association between farm exposure and atopy, according to the CD14 C-159T polymorphism. *J Allergy Clin Immunol* 2006;118:658-65.
- Bieli C, Eder W, Frei R, Braun-Fahrlander C, Klimecki W, Waser M, et al. A polymorphism in CD14 modifies the effect of farm milk consumption on allergic diseases and CD14 gene expression. *J Allergy Clin Immunol* 2007;120:1308-15.
- Heinzmann A, Mao XQ, Akaiwa M, Kreomer RT, Gao PS, Ohshima K, et al. Genetic variants of IL-13 signalling and human asthma and atopy. *Hum Mol Genet* 2000;9:549-59.
- Kim HB, Lee YC, Lee SY, Jung J, Jin HS, Kim JH, et al. Gene-gene interaction between IL-13 and IL-13Ralpha1 is associated with total IgE in Korean children with atopic asthma. *J Hum Genet* 2006;51:1055-62.
- He JQ, Chan-Yeung M, Becker AB, Dimich-Ward H, Ferguson AC, Manfreda J, et al. Genetic variants of the IL13 and IL4 genes and atopic diseases in at-risk children. *Genes Immun* 2003;4:385-9.
- Huebner M, Kim DY, Ewart S, Karmaus W, Sadeghnejad A, Arshad SH. Patterns of GATA3 and IL13 gene polymorphisms associated with childhood rhinitis and atopy in a birth cohort. *J Allergy Clin Immunol* 2008;121:408-14.
- Kim JJ, Min JY, Lee JH. Polymorphisms in the IL-13 and IL-4 receptor alpha genes and allergic rhinitis. *Eur Arch Otorhinolaryngol* 2007;264:395-9.
- Hong SJ. Korean ISAAC Study Group of Korean Association of Allergy and Respiratory Diseases. Report of Korean ISAAC epidemiologic study for asthma and allergic diseases in children. *Pediatr Allergy Respir Dis (Korea)* 2007;17(suppl 1):S55-66.
- Hong SJ AK, Lee SY, Kim KE. The prevalences of asthma and allergic diseases in Korean children. *Korean J Pediatr* 2008;51:343-50.
- Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multi-country cross-sectional surveys. *Lancet* 2006;368:733-43.
- Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). *Pediatr Allergy Immunol* 2004;15:72-8.
- Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998;101:587-93.
- Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol* 1995;95:1179-90.
- Cohet C, Cheng S, MacDonald C, Baker M, Foliaki S, Huntington N, et al. Infections, medication use, and the prevalence of symptoms of asthma, rhinitis, and eczema in childhood. *J Epidemiol Community Health* 2004;58:852-7.
- Newson RB, Shaheen SO, Chinn S, Burney PG. Paracetamol sales and atopic disease in children and adults: an ecological analysis. *Eur Respir J* 2000;16:817-23.
- Droste JH, Wieringa MH, Weyler JJ, Nelen VJ, Vermeire PA, Van Bever HP. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy* 2000;30:1547-53.
- Johnson CC, Ownby DR, Alford SH, Havstad SL, Williams LK, Zoratti EM, et al. Antibiotic exposure in early infancy and risk for childhood atopy. *J Allergy Clin Immunol* 2005;115:1218-24.
- Barragan-Mejia MM, Morfin-Maciell B, Nava-Ocampo AA. A Mexican population-based study on exposure to paracetamol and the risk of wheezing, rhinitis, and eczema in childhood. *J Invest Allergol Clin Immunol* 2006;16:247-52.
- Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. *Indoor Air* 2007;17:284-96.
- Douwes J, van Strien R, Doekes G, Smit J, Kerkhof M, Gerritsen J, et al. Does early indoor microbial exposure reduce the risk of asthma? The Prevention and Incidence of Asthma and Mite Allergy birth cohort study. *J Allergy Clin Immunol* 2006;117:1067-73.
- Custovic A, Simpson BM, Simpson A, Hallam C, Craven M, Brutsche M, et al. Manchester Asthma and Allergy Study: low-allergen environment can be achieved and maintained during pregnancy and in early life. *J Allergy Clin Immunol* 2000;105:252-8.
- Halmerbauer G, Gartner C, Schier M, Arshad H, Dean T, Koller DY, et al. Study on the prevention of allergy in Children in Europe (SPACE): allergic sensitization in children at 1 year of age in a controlled trial of allergen avoidance from birth. *Pediatr Allergy Immunol* 2002;13(suppl 15):47-54.
- Kleeberger SR, Peden D. Gene-environment interactions in asthma and other respiratory diseases. *Annu Rev Med* 2005;56:383-400.
- Denning DW, O'Driscoll BR, Hogaboam CM, Bowyer P, Niven RM. The link between fungi and severe asthma: a summary of the evidence. *Eur Respir J* 2006;27:615-26.
- Kobayashi T, Iijima K, Radhakrishnan S, Mehta V, Vassallo R, Lawrence CB, et al. Asthma-related environmental fungus, *Alternaria*, activates dendritic cells and produces potent Th2 adjuvant activity. *J Immunol* 2009;182:2502-10.
- Matsuaki Y, Wada K, White TA, Benson LM, Charlesworth MC, Checkel JL, et al. Recognition of fungal protease activities induces cellular activation and eosinophil-derived neurotoxin release in human eosinophils. *J Immunol* 2009;183:6708-16.
- Piau JP, Massot C, Moreau D, Ait-Khaled N, Bouayad Z, Mohammad Y, et al. Assessing allergic rhinitis in developing countries. *Int J Tuberc Lung Dis* 2010;14:506-12.
- Zhao J, Bai J, Shen K, Xiang L, Huang S, Chen A, et al. Self-reported prevalence of childhood allergic diseases in three cities of China: a multicenter study. *BMC Public Health* 2010;10:551.

TABLE E1. Frequency of the *IL13+2044G/A* polymorphism in Korean children (Seoul) according to current AR and atopy

<i>IL13</i>	Current AR (–)		Current AR (+)					Current AR with atopy					Current AR without atopy				
	No.	Percent	No.	Percent	aOR	95% CI	P value	No.	Percent	aOR	95% CI	P value	No.	Percent	aOR	95% CI	P value
GG	326	48	115	46	1.00			73	50	1.00			40	42	1.00		
GA	295	43	112	45	0.98	0.71-1.36	.92	62	42	0.84	0.56-1.25	.38	47	49	1.19	0.74-1.93	.46
AA	60	9	21	8	0.90	0.50-1.63	.72	12	8	0.72	0.33-1.55	.40	9	9	1.31	0.59-2.92	.51
GG	326	48	115	46	1.00			73	50	1.00			40	42	1.00		
GA+AA	355	52	133	54	0.97	0.71-1.33	.85	74	50	0.82	0.56-1.20	.31	56	58	1.21	0.77-1.91	.41

Data were analyzed by using logistic regression, adjusting for age, sex, and family history of AR.

TABLE E2. aORs and 95% CIs for current AR and the interaction between mold exposure during infancy and the *IL13*+2044G/A polymorphism in Korean children (Seoul)

<i>IL13</i>	Current AR (–)		Current AR with atopy					Current AR without atopy				
	No.	Percent	No.	Percent	aOR	95% CI	P value	No.	Percent	aOR	95% CI	P value
Mold exposure (no) and <i>IL13</i> (GG)	264	43	56	42				30	34			
Mold exposure (no) and <i>IL13</i> (GG+GA)	294	47	52	39	0.71	0.46-1.12	.14	41	47	1.16	0.68-1.96	.59
Mold exposure (yes) and <i>IL13</i> (GG)	32	5	8	6	1.04	0.43-2.52	.93	6	7	1.43	0.52-3.90	.49
Mold exposure (yes) and <i>IL13</i> (GA+AA)	29	5	16	12	2.95	1.42-6.12	.00	11	13	3.66	1.57-8.53	.00

Data were analyzed by using logistic regression, adjusting for age, sex and family history of AR.

TABLE E3. aORs and 95% CIs for current AR and the interaction between antibiotics during infancy and the *IL13*+2044G/A polymorphism in Korean children (Seoul)

<i>IL13</i>	Current AR (–)		Current AR (+)				<i>P</i> value
	No.	Percent	No.	Percent	aOR	95%CI	
Antibiotics (no) and <i>IL13</i> (GG)	232	35.69	67	28.15			
Antibiotics (no) and <i>IL13</i> (GG+GA)	225	34.62	71	29.83	0.97	0.64-1.48	.89
Antibiotics (yes) and <i>IL13</i> (GG)	82	12.62	43	18.07	1.57	0.95-2.58	.08
Antibiotics (yes) and <i>IL13</i> (GA+AA)	111	17.08	57	23.95	1.34	0.84-2.14	.22

Data were analyzed by using logistic regression, adjusting for age, sex and family history of AR.

TABLE E4. aORs and 95% CIs for current AR and the interaction between moving to a newly built house during infancy and *IL13+2044G/A* polymorphism in Korean children (Seoul)

	Current AR (–)		Current AR (+)				<i>P</i> value
	No.	Percent	No.	Percent	aOR	95% CI	
<i>IL13</i>							
Move to a newly built house (no) and <i>IL13</i> (GG)	274	40.83	103	42.56			
Move to a newly built house (no) and <i>IL13</i> (GG+GA)	303	45.16	110	45.45	0.87	0.62-1.22	.43
Move to a newly built house (yes) and <i>IL13</i> (GG)	46	6.86	8	3.31	0.45	0.20-1.03	.06
Move to a newly built house (yes) and <i>IL13</i> (GA+AA)	48	7.15	21	8.68	1.04	0.57-1.91	.90

Data were analyzed by using logistic regression, adjusting for age, sex, and family history of AR.

TABLE E5. Comparison of the characteristics between subjects with complete data and subjects with incomplete data

Characteristics	Total	Complete data	Incomplete data	P value
No.	4554	2732 (60.0%)	1822 (40.0%)	
Age (y), mean $\pm$ SD	9.50 $\pm$ 1.73	9.54 $\pm$ 1.72	9.40 $\pm$ 1.76	.013
Sex (M/F)	2317/2237	1396/1336	921/901	.717
BMI (kg/m ²), mean $\pm$ SD	17.91 $\pm$ 3.14	17.87 $\pm$ 3.03	18.03 $\pm$ 3.44	.178
Maternal educational degree (> high school)	2690/4423 (60.8%)	1764/2732 (64.6%)	926/1691 (54.8%)	<.001
Economic status (monthly income)				
Low ($\leq$ 1999 USD)	554/4382 (12.6%)	291/2662 (10.9%)	263/1720 (15.3%)	<.001
Middle (2000-4999 USD)	3209/4382 (73.2%)	1968/2662 (73.9%)	1241/1720 (72.2%)	
High ($\geq$ 5000 USD)	619/4382 (14.1%)	403/2662 (15.1%)	216/2662 (12.6%)	
Parental history of allergic diseases (asthma, AR, or AD)	1458/3882 (37.6%)	1050/2732 (38.4%)	408/1150 (35.5%)	.088
Environmental tobacco smoke	1721/4442 (38.7%)	1005/2732 (36.8%)	716/1710 (41.9%)	.001
Location of school				
Downtown	734/4554 (16.1%)	249/2732 (9.1%)	485/1822 (26.6%)	<.001
Northeastern	794/4554 (17.4%)	598/2732 (21.9%)	196/1822 (10.8%)	
Northwestern	1023/4554 (22.5%)	713/2732 (26.1%)	310/1822 (17.0%)	
Southeastern	1242/4554 (27.3%)	870/2732 (31.8%)	372/1822 (20.4%)	
Southwestern	761/4554 (16.7%)	302/2732 (11.1%)	459/1822 (25.2%)	

AD, Atopic dermatitis; BMI, body mass index; F, female; M, male; USD, US dollar.