



## A rhinitis phenotype associated with increased development of bronchial hyperresponsiveness and asthma in children

Eun Lee, MD, PhD <sup>\*</sup>; Si Hyeon Lee, BS <sup>†</sup>; Ji-Won Kwon, MD, PhD <sup>‡</sup>; Yeongho Kim, MD <sup>§</sup>; Hyun-Ju Cho, MD <sup>||</sup>; Song-I Yang, MD, PhD <sup>¶</sup>; Young-Ho Jung, MD, PhD <sup>\*\*</sup>; Hyung Young Kim, MD <sup>††</sup>; Ju-Hee Seo, MD <sup>‡‡</sup>; Byoung-Ju Kim, MD, PhD <sup>§§</sup>; Hyo Bin Kim, MD, PhD <sup>|||</sup>; So Yeon Lee, MD, PhD <sup>¶¶</sup>; Ho-Jang Kwon, MD, PhD <sup>¶¶</sup>; Soo-Jong Hong, MD, PhD <sup>||</sup>

<sup>\*</sup> Department of Pediatrics, Inje University Haeundae Paik Hospital, Busan, Korea

<sup>†</sup> Asan Institute for Life Sciences, University of Ulsan College of Medicine, Seoul, Korea

<sup>‡</sup> Department of Pediatrics, Seoul National University Bundang Hospital, Seongnam, Korea

<sup>§</sup> Department of Pediatrics, Gyeongsang National University Changwon Hospital, Changwon, Korea

<sup>||</sup> Department of Pediatrics, Childhood Asthma and Atopy Center, Environmental Health Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

<sup>¶</sup> Department of Pediatrics, Hallym University Sacred Heart Hospital, Anyang, Korea

<sup>\*\*</sup> Department of Pediatrics, CHA University School of Medicine, Seongnam, Korea

<sup>††</sup> Department of Pediatrics, Pusan National University Yangsan Hospital, Yangsan, Korea

<sup>‡‡</sup> Department of Pediatrics, Dankook University College of Medicine, Seoul, Korea

<sup>§§</sup> Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio

<sup>|||</sup> Department of Pediatrics, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

<sup>¶¶</sup> Department of Preventive Medicine, Dankook University College of Medicine, Cheonan, Korea

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### ABSTRACT

**Background:** Allergic rhinitis (AR) has a wide range of clinical features and may be accompanied by comorbid allergic diseases.

**Objectives:** To identify rhinitis phenotypes in school aged children and to predict the prognosis for developing bronchial hyperresponsiveness (BHR) and asthma.

**Methods:** This prospective follow-up study involved schoolchildren from the Children's Health and Environment Research cohort with current rhinitis, which was defined based on parental-reported, physician-diagnosed rhinitis and symptoms of rhinitis in the previous 12 months. All participants were followed up at 2 and 4 years later. Rhinitis clusters were identified by latent class analysis that used demographic, clinical, and environmental variables.

**Results:** In 512 eligible children (age range, 6–8 years), 4 rhinitis phenotypes were identified: cluster 1 (25% of children) was associated with nonatopy and a low socioeconomic status; cluster 2 (36%) was associated with a high-atopic burden but normal lung function; cluster 3 (22%) was associated with a high-atopic burden and impaired lung function; and cluster 4 (17%) was associated with low atopy and a high socioeconomic status. Cluster 3 was associated with the highest total serum IgE levels and blood eosinophil percentages at enrollment and the highest incidence of new cases of BHR ( $P = .04$ ) and asthma symptoms ( $P = .005$ ) during follow-up.

**Conclusion:** The rhinitis cluster of schoolchildren with atopy and impaired lung function is associated with allergic march. This identification of distinct rhinitis phenotypes in affected children may help to prevent allergic march in children with rhinitis.

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**Reprints:** Soo-Jong Hong, MD, PhD, Department of Pediatrics, Childhood Asthma and Atopy Center, Environmental Health Center, Asan Medical Center, College of Medicine, University of Ulsan, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea; E-mail: [sjhong@amc.seoul.kr](mailto:sjhong@amc.seoul.kr).

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### Introduction

Approximately 40% of children develop allergic rhinitis (AR), which has been increasing in prevalence in recent years.<sup>1,2</sup> Although AR is not considered to be life-threatening, its societal and economic effect in children is grossly underestimated. Moreover, AR in children affects their quality of life, including sleep impairment and even cognitive and psychomotor functions.<sup>1</sup> Moreover, children with AR have an increased risk of developing adult asthma.<sup>3</sup>

Defining rhinitis phenotypes would be useful because different rhinitis clusters might reflect disparate pathophysiologic features. Such phenotyping could facilitate the development of personalized therapies for each phenotype and might prevent the development of other allergic diseases. Several attempts have been made to classify rhinitis phenotypes based on disease severity, temporal patterns (eg, seasonal or perennial type), and main symptoms (eg, runny nose or nasal blockage).<sup>4–6</sup> However, rhinitis phenotypes remain poorly defined, and classifications based on only one aspect among diverse pathophysiologic features do not reflect the entire spectrum of this disorder.

The term “allergic march” refers to the progression of allergic diseases that typically begins with atopic dermatitis (AD) and then progresses to asthma and/or AR.<sup>7</sup> Notably, AR often precedes asthma and is a risk factor for its development.<sup>8</sup> Common genetic and environmental risk factors may partially account for the occurrence of allergic march.<sup>9</sup> It is therefore important to identify the features of the preceding conditions that are associated with the allergic march because this may help in identifying individuals who should be targeted for the prevention of the subsequent development of other allergic diseases.

Cluster analyses have been used to identify disease subgroups among clinically and pathophysiologically heterogeneous diseases. This study aimed to define rhinitis phenotypes in school-aged children using latent class analysis and to determine whether these phenotypes were associated with the allergic march. In addition, we evaluated the risk factors and prognosis of allergic march associated with each rhinitis phenotype.

## Methods

### Study Population

This prospective cohort study was conducted as part of the Children's Health and Environment Research (CHEER) study among children from elementary schools in Korea during 4 years between January 2006 and December 2010. The CHEER cohort children were surveyed based on a parent-completed questionnaire, skin prick test (SPT), total serum IgE level measurement, and lung function and methacholine challenge tests at the time of enrollment and 2 and 4 years later. Additional details of this study design were described previously.<sup>10</sup> Among a total of 2,491 children in CHEER who underwent SPT, 512 participants who had current rhinitis were included in our present study (eFig 1). Among the remaining 1,979 children who did not have current rhinitis at the time of enrollment, 371 lacked symptoms of rhinitis both before enrollment and during follow-up and were included as the control group in this study. Current rhinitis was defined as rhinitis that was reported by a parent and diagnosed by a physician before the first survey, and symptoms that were not related to respiratory infection in the preceding 12 months. Symptoms of rhinitis included sneezing, runny nose, and/or nasal stuffiness that were not related to respiratory infection within the 12 months preceding the first survey. Written informed consent was obtained from the parents or guardians of all study participants. The study protocol was approved by the institutional review board of the University of Ulsan College of Medicine.

### Questionnaire

The International Studies of Asthma Allergic diseases in Childhood (ISAAC) questionnaire has been validated in Korean children and was used to evaluate the presence and the risk factors of allergic diseases, including AD, AR, and asthma in each survey.<sup>11,12</sup> A participant was determined to have asthma at the time of enrollment if there was an affirmative response to the following question in the ISAAC questionnaire: “Have you ever been diagnosed with

asthma by a physician?” The presence of asthma symptoms in the preceding 12 months was assessed with the question, “Have you ever had symptoms of asthma, such as wheezing or whistling in the chest, during the last 12 months?”

The prevalence of food allergy was defined as yes based on the following questions: “In the past 12 months, did your child have any symptoms of food allergy? (past year food allergy symptoms),” “Has your child experienced symptoms of food allergy? (food allergy symptom ever),” “Has your child been diagnosed with food allergy by a physician? (lifetime food allergy diagnosis),” and “In the past 12 months, has your child been treated because of symptoms of food allergy? (treatment of food allergy in the past 12 months).”

The prevalence of AD was defined as yes based on the following questions: “Did your child have eczema with itching in the previous 12 months? (past year AD symptoms),” “Has your child experienced eczema in combination with itching for at least 6 months? (AD symptom ever),” “Has your child been diagnosed with AD by a physician (lifetime AD diagnosis),” and “In the past 12 months, has your child been treated due to AD? (treatment of AD in the past 12 months).”

### Evaluation of Allergy: SPT and Total Serum IgE

SPT was performed for 13 common inhalant allergens: *Derma-tophagoides pteronyssinus*, *Dermatophagoides farinae* (*D farinae*), dog dander, cat epithelium, cockroach, *Alternaria alternata*, *Aspergillus fumigatus*, grass pollen mixture, tree mixture, ragweed, mugwort, alder, and oak, and 4 food allergens: peanut, egg white, cow's milk, and soybean.<sup>11</sup> Histamine (10 mg/mL) and normal saline were used as positive and negative controls, respectively. A positive SPT result was defined as the development of a mean wheal size of 3 mm or greater and a wheal response to histamine after 15 minutes. Atopy was defined as at least 1 positive SPT response. Total serum IgE levels were measured using the AutoCAP fluorescent enzyme immunoassay system (Phadia AB, Uppsala, Sweden) with a lower limit of detection for total serum IgE at 2 kU/L.

### Lung Function Test and Bronchial Hyperresponsiveness

Spirometry was performed according to the American Thoracic Society and European Respiratory Society guidelines using a portable microspirometer (Microspiro HI-298; Chest Corporation, Tokyo, Japan).<sup>11,13,14</sup> Forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC (FEF<sub>25%–75%</sub>) were measured. The cumulative dose of methacholine that caused a 20% reduction in FEV<sub>1</sub> (PC<sub>20</sub>) was calculated according to the American Thoracic Society recommendations.<sup>15</sup> Details of bronchial hyperresponsiveness (BHR) measurements were described previously.<sup>10</sup> To strictly exclude false-positive BHR results, participants were determined to have BHR to methacholine when the methacholine PC<sub>20</sub> was 8 mg/mL or less.<sup>15</sup> Newly developed BHR was defined as conversion from a negative BHR test result at enrollment to a positive BHR test result at the time of the 4-year follow-up survey.

### Cluster Analysis

Current rhinitis phenotypes were identified using latent class analysis, which was previously used to identify asthma phenotypes<sup>16</sup>; this statistical method can classify distinct subclasses based on observed heterogeneities in a population. The following variables were used to infer rhinitis clusters among children with rhinitis at the time of enrollment without observers' supervision: demographic characteristics, including sex, body mass index; socioeconomic status, including income and maternal educational level; environmental factors, including prior exposure to environmental tobacco smoke (ETS); parental history of allergic

diseases (AD, AR, and/or asthma); presence of allergic disease; comorbidities at the time of enrollment; treatment of rhinitis within the previous 12 months; SPT, total serum IgE, blood eosinophil percentages, and pulmonary function test results at the time of enrollment; and the presence of rhinitis at the time of enrollment. To determine the optimal number of clusters, we selected the lowest bayesian information criterion,<sup>17</sup> which defined 4 rhinitis clusters in this study. The predicted FEV<sub>1</sub>, FEV<sub>1</sub>/FVC, and FEF<sub>25%–75%</sub> were dichotomized as 80% or greater and less than 80%.

#### Assessment of Prognosis

The association of clusters with the allergic march was determined by assessing the number of participants with newly developed BHR, asthma symptoms, or asthma diagnosis during follow-up. This information was also obtained for the control group. Data from the 4-year follow-up were used for analysis. A participant was determined to have newly developed asthma during follow-up if the answers to the ISAAC question, “Has your child ever been diagnosed with asthma by a physician?” were no at the time of enrollment and yes at the 4-year follow-up. A participant was determined to have newly developed asthma symptoms during follow-up if the answers to the ISAAC question, “Did your child have any symptoms of asthma such as wheezing or whistling in the chest during the last 12 months?” were no at the time of enrollment and yes at the 4-year follow-up. Newly developed BHR was defined as conversion from a negative BHR test result at the time of enrollment to a positive BHR test result at the 4-year follow-up.

#### Statistical Analysis

To compare the characteristics at enrollment across clusters, including the control group, and to determine the prevalence of newly developed BHR, asthma symptoms, and asthma diagnosis during follow-up, the *t* test, Fisher exact test, or Kruskal-Wallis test was used, where appropriate. The Bonferroni correction for multiple testing was used for continuous variables. Because the distribution of total serum IgE levels was skewed, data were log-transformed to approximate a normal distribution. Statistical analyses were performed using SAS statistical software for Windows,

version 9.2 (SAS Institute Inc, Cary, North Carolina), and *P* < .05 was considered statistically significant.

#### Results

No significant differences were found in the baseline characteristics between the participants who were followed up for 4 years and those who were initially included but were not followed up for 4 years (eTable 1). Table 1 gives the demographic and clinical characteristics of 512 children with current rhinitis and 371 asymptomatic controls at the time of enrollment, which included SPT results, parental history of allergic diseases, and BHR and asthma diagnoses. The children with current rhinitis were also compared with 1,979 children without a diagnosis of current rhinitis at the time of enrollment (eTable 1).

#### Current Rhinitis Cluster Characteristics

Cluster analysis of the school-aged children with current rhinitis revealed 4 clusters. Cluster 1 (*n* = 127 [24.8%]) had a very low prevalence of atopy and low socioeconomic status, whereas cluster 2 (*n* = 186 [36.3%]) had a high prevalence of atopy and normal lung function. In contrast, cluster 3 (*n* = 112 [21.9%]) had a high prevalence of atopy and impaired lung function. Finally, cluster 4 (*n* = 87 [17.0%]) had a low prevalence of atopy and high socioeconomic status. The prevalence of food allergy symptoms both during the lifetime and in the previous 12 months was significantly higher in cluster 3 (*P* < .001) (Table 2). In addition, this cluster had significantly higher prevalences of lifetime AD diagnosis and symptoms and treatment of AD in the previous 12 months (Table 3).

#### Allergic Burden of the 4 Rhinitis Clusters and Control Group

At the time of enrollment, cluster 3 had the highest mean (SD) percentage of blood eosinophils (5.8% [2.6%]) and total serum IgE levels (616.04 [85.67] kUA/L), followed in a decreasing order by clusters 2, 4, and 1 (Fig 1A and B). No significant difference in blood eosinophil percentages was found between clusters 2 and 3. In addition, cluster 3 had a significantly lower mean percentage of predicted FEV<sub>1</sub> at the time of enrollment than both the other

**Table 1**  
Demographic and Clinical Characteristics of the Study Cohort at Enrollment

| Characteristic                                           | No. (%) of Patients by Cluster |                         |                            |                            | No. (%) of Controls <sup>a</sup> |
|----------------------------------------------------------|--------------------------------|-------------------------|----------------------------|----------------------------|----------------------------------|
|                                                          | 1                              | 2                       | 3                          | 4                          |                                  |
| Total                                                    | 127 (24.8)                     | 186 (36.3)              | 112 (21.9)                 | 87 (17.0)                  | 370                              |
| Male sex                                                 | 89 (70) <sup>b</sup>           | 101 (54) <sup>b,c</sup> | 61 (54) <sup>c</sup>       | 47 (54) <sup>c</sup>       | 166 (45)                         |
| Normal BMI                                               | 110 (87)                       | 159 (85)                | 91 (81)                    | 73 (84)                    | 316 (85)                         |
| Parental history of allergic diseases                    | 50 (39) <sup>b</sup>           | 89 (48) <sup>b</sup>    | 58 (52) <sup>b</sup>       | 37 (43) <sup>b</sup>       | 95 (26)                          |
| Income <US\$3,000                                        | 94 (74) <sup>b</sup>           | 121 (65)                | 89 (80)                    | 16 (18) <sup>b,c,d,e</sup> | 270 (73)                         |
| Maternal educational level of high school or less        | 88 (69) <sup>b</sup>           | 92 (50) <sup>b,c</sup>  | 79 (71)                    | 0 (0) <sup>b,c,d,e</sup>   | 239 (64)                         |
| Exposure to ETS                                          | 72 (57) <sup>b</sup>           | 73 (39) <sup>c</sup>    | 52 (46)                    | 14 (16) <sup>b,c,d,e</sup> | 158 (43)                         |
| Rhinitis treatment in the previous 12 months             | 105 (83) <sup>b</sup>          | 167 (90) <sup>b</sup>   | 110 (98) <sup>b,c,d</sup>  | 71 (82) <sup>b,d</sup>     | 0 (0)                            |
| Atopy                                                    | 2 (2) <sup>b</sup>             | 92 (50) <sup>b,c</sup>  | 79 (71) <sup>b,c,d</sup>   | 32 (37) <sup>b,c,d</sup>   | 62 (17)                          |
| Total serum IgE ≥100 kUA/L                               | 48 (38) <sup>b</sup>           | 106 (57) <sup>b,c</sup> | 95 (85) <sup>b,c,d</sup>   | 39 (45) <sup>d,e</sup>     | 143 (39)                         |
| Eosinophils ≥4%                                          | 14 (11) <sup>c</sup>           | 84 (45) <sup>b,c</sup>  | 86 (77) <sup>b,d,c</sup>   | 43 (49) <sup>b,c,d</sup>   | 89 (24)                          |
| AD diagnosis, ever                                       | 29 (23)                        | 73 (39) <sup>b,c</sup>  | 78 (70) <sup>b,c,d</sup>   | 55 (63) <sup>b,c,d</sup>   | 89 (24)                          |
| Asthma diagnosis, ever                                   | 18 (14) <sup>b</sup>           | 29 (16) <sup>b</sup>    | 26 (23) <sup>b</sup>       | 22 (25) <sup>b</sup>       | 22 (6)                           |
| PC <sub>20</sub> on methacholine challenge test ≤8 mg/mL | 24 (19)                        | 37 (20)                 | 44 (39) <sup>b,c,d</sup>   | 11 (13) <sup>e</sup>       | 59 (16)                          |
| FEV <sub>1</sub> ≥80%                                    | 121 (95)                       | 184 (99) <sup>b,c</sup> | 102 (91) <sup>d</sup>      | 86 (99) <sup>e</sup>       | 350 (94)                         |
| FEV <sub>1</sub> /FVC ≥80%                               | 125 (98)                       | 184 (99) <sup>b</sup>   | 98 (87.5) <sup>b,c,d</sup> | 86 (99) <sup>e</sup>       | 354 (95)                         |
| FEF <sub>25%–75%</sub> ≥80%                              | 78 (61)                        | 129 (69) <sup>b,c</sup> | 39 (3) <sup>b,c,d</sup>    | 61 (70) <sup>d,e</sup>     | 244 (66)                         |

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BMI, body mass index; ETS, environmental tobacco smoke; FEF<sub>25%–75%</sub>, forced expiratory flow between 25% and 75%; FEV<sub>1</sub>, forced expiratory volume in 1 second; PC<sub>20</sub>, concentration of methacholine needed to lead to a 20% reduction in FEV<sub>1</sub> from baseline.

<sup>a</sup>The control group included children from the Children's Health and Environment Research study who underwent skin prick tests but lacked symptoms of rhinitis both before enrollment and during follow-up.

<sup>b</sup>*P* < .05 compared with the control group.

<sup>c</sup>*P* < .05 compared with cluster 1.

<sup>d</sup>*P* < .05 compared with cluster 2.

<sup>e</sup>*P* < .05 compared with cluster 3.

**Table 2**  
Prevalence of Food Allergy According to the Rhinitis Clusters

| Variable                                        | No. (%) of Control | No. (%) of Patients by Cluster |                            |                                |                           |
|-------------------------------------------------|--------------------|--------------------------------|----------------------------|--------------------------------|---------------------------|
|                                                 |                    | 1                              | 2                          | 3                              | 4                         |
| Food allergy symptom ever                       | 22/345 (6.0)       | 23/124 <sup>a</sup> (18.5)     | 32/185 <sup>a</sup> (17.3) | 26/111 <sup>a</sup> (23.4)     | 16/87 <sup>a</sup> (18.4) |
| Past-year food allergy symptoms                 | 9/367 (2.5)        | 17/124 <sup>a</sup> (13.7)     | 22/185 <sup>a</sup> (11.9) | 20/111 <sup>a</sup> (18.0)     | 5/87 <sup>d</sup> (5.7)   |
| Lifetime food allergy diagnosis                 | 14/367 (3.8)       | 10/123 (8.1)                   | 20/185 <sup>a</sup> (10.8) | 11/111 <sup>a</sup> (9.9)      | 8/87 <sup>a</sup> (9.2)   |
| Treatment of food allergy in the past 12 months | 7/366 (1.9)        | 7/123 <sup>a</sup> (5.7)       | 9/184 (4.9)                | 15/111 <sup>a,b,c</sup> (13.5) | 3/87 <sup>d</sup> (3.4)   |

<sup>a</sup>P < .05 compared with the control group.

<sup>b</sup>P < .05 compared with cluster 1.

<sup>c</sup>P < .05 compared with cluster 2.

<sup>d</sup>P < .05 compared with cluster 3.

clusters and the control group (Fig 1C); however, clusters 1 and 4 did not have significant differences in this variable compared with the control group. Significant differences were found in the rates of SPT responses to both indoor and outdoor allergens at the time of enrollment: cluster 3 had a significantly higher prevalence of atopy to indoor allergens among the rhinitis clusters and control group at the time of enrollment and follow-up (Fig 2A and B). In addition, the sensitization rate against outdoor allergens was also higher in cluster 3 compared with cluster 1 and the control group at the time of enrollment (Fig 2C). No significant differences were observed in the sensitization rate to outdoor allergens between clusters 2 and 3 at the time of enrollment. In addition, no significant difference in the sensitization rate to outdoor allergens between clusters 2 and 3 was observed at follow-up (Fig 2D).

#### Associations Between Allergic March and Demographic and Environmental Factors

Associations between progression to BHR or asthma symptoms and specific demographic or environmental factors were determined by multivariate logistic regression analysis, which determined that none of the tested variables were significantly associated with allergic march variables (data not shown).

#### Prognosis of Rhinitis Clusters

During the prospective 4-year follow-up period, cluster 3 had the highest prevalence of individuals with newly developed BHR, although there was no significant difference between clusters 2 (10.4%) and 3 (17.1%) (Fig 3A). In addition, cluster 3 had the highest prevalence of individuals with newly developed asthma symptoms, but there was no significant difference between clusters 2 (13.5%) and 3 (16.4%) (Fig 3B). However, no significant differences were found in the prevalence of new cases of physician-diagnosed asthma based on the questionnaire (data not shown).

#### Discussion

Cluster analysis of rhinitis in school-aged children may allow for division of the heterogeneous clinical spectrum of childhood

rhinitis into more homogeneous clusters. Subsequent identification of independent risk factors that are associated with each cluster may help in elucidating the pathophysiologic mechanisms underlying each cluster. In this prospective cohort study of a general population of school-aged children, 4 distinct clusters of participants with current rhinitis were identified. A high prevalence of atopy was observed in 2 of the clusters. However, the 2 clusters differed in lung function; cluster 2 had a higher prevalence of normal lung function, whereas impaired lung function was more prevalent in cluster 3. The other 2 clusters (clusters 1 and 4) had very low or low prevalence of atopy; however, they differed in socioeconomic status. Specifically, clusters 1 had a higher prevalence of individuals with a low socioeconomic status, whereas the prevalence of those with higher socioeconomic status was higher in cluster 4. The highly atopic cluster with impaired lung function was associated with an increased prevalence of newly developed BHR and asthma symptoms during follow-up, although this finding was not statistically significant. The significantly higher prevalence of food allergy and AD in cluster 3 provides further evidence of a high risk of allergic march in these particular children.

Several studies have sought to classify rhinitis based on the allergic status, associated symptoms, and severity with observer bias.<sup>4,6,18</sup> Because rhinitis phenotypes are based on both the clinical characteristics and underlying pathophysiologic mechanisms, this artificial classification of rhinitis is unlikely to fully define its broad spectrum. In the Isle of Wight birth cohort study, a total of 13 variables were used to identify rhinitis phenotypes.<sup>19</sup> These variables consisted of answers to a questionnaire along with objective evaluations, SPT responses, lung function tests, BHR, and physician-diagnosed rhinitis. Another study found that severe, early-onset rhinitis was associated with nearly simultaneous onset of asthma.<sup>20</sup> However, the Isle of Wight birth cohort study was performed in young adults, and asthma comorbidities were only evaluated retrospectively. In contrast, the present study consisted of school-aged children with rhinitis, and we prospectively investigated the development of new cases of BHR and asthma symptoms during the 4-year follow-up period. Along with the

**Table 3**  
Prevalence of Atopic Dermatitis According to the Rhinitis Clusters

| Variable                              | No. (%) of Controls | No. (%) of Patients by Cluster |                              |                                |                               |
|---------------------------------------|---------------------|--------------------------------|------------------------------|--------------------------------|-------------------------------|
|                                       |                     | 1                              | 2                            | 3                              | 4                             |
| Lifetime AD diagnosis                 | 89/366 (24.3)       | 29/124 (23.4)                  | 73/186 <sup>a,b</sup> (39.2) | 78/112 <sup>a,b,c</sup> (69.6) | 55/87 <sup>a,b,c</sup> (63.2) |
| Treatment of AD in the past 12 months | 32/367 (8.7)        | 13/115 (11.3)                  | 36/161 <sup>a,b</sup> (22.4) | 42/94 <sup>a,b,c</sup> (44.7)  | 18/70 <sup>a,b,d</sup> (25.7) |
| AD symptom ever                       | 104/366 (28.4)      | 43/124 (34.7)                  | 80/186 <sup>a</sup> (43.0)   | 82/112 <sup>a,b,c</sup> (73.2) | 55/87 <sup>a,b,c</sup> (63.2) |
| Past-year AD symptoms                 | 65/366 (17.8)       | 25/124 (20.2)                  | 56/186 <sup>a</sup> (30.1)   | 60/112 <sup>a,b,c</sup> (53.6) | 34/87 <sup>a,b,d</sup> (39.1) |

Abbreviation: AD, atopic dermatitis.

<sup>a</sup>P < .05 compared with the control group.

<sup>b</sup>P < .05 compared with cluster 1.

<sup>c</sup>P < .05 compared with cluster 2.

<sup>d</sup>P < .05 compared with cluster 3.

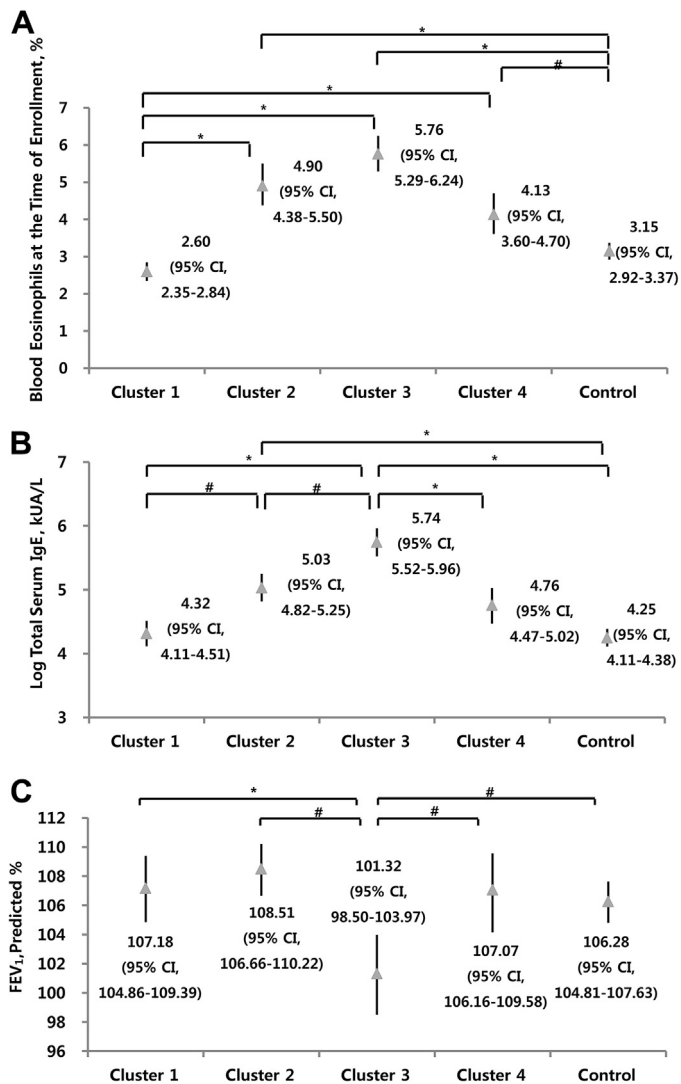


**Figure 1.** Blood eosinophil percentage (A), log-transformed total serum IgE levels (B), and forced expiratory volume in 1 second (FEV<sub>1</sub>) predicted percentage (C) at enrollment. Mean ( $\Delta$ ) and 95% confidence intervals (CIs) (error bars) are shown. There were no significant differences unless indicated. Kruskal-Wallis tests were used because the normality assumption in the residuals was violated. The Bonferroni correction for multiple testing was applied for continuous variables. \* $P < 0.001$ , # $P < 0.05$ .

biomarkers used by the Isle of Wight study, we also included environmental factors, such as socioeconomic status and ETS exposure, in this cluster analysis.

Although the prevalence of ETS exposure in this study was higher than that reported in other countries,<sup>19</sup> it was consistent with that of a previous study in Korea.<sup>21</sup> Because exposure to ETS is associated with low educational and/or income levels,<sup>21–23</sup> the complex interactions among these variables might differently affect the rhinitis phenotypes, promoting distinct pathophysiologic mechanisms that shape susceptibility to specific phenotypes. Thus, the use of these variables in cluster analysis might aid in revealing rhinitis clusters that differ in underlying pathophysiologic mechanisms.<sup>24</sup> The participants in previous rhinitis studies and the participants of this study differed in age and ethnicity; thus, the rhinitis phenotypes in school-aged children identified herein were different than those previously reported.

BHR, one of the characteristics of asthma, can also be observed in patients with AR but without asthma.<sup>8,25</sup> Although

the relevance of BHR in individuals with rhinitis who do not have symptoms of asthma remains unclear, several studies found that BHR was associated with asthma development in participants with AR.<sup>8,26</sup> Another study also reported that AR was more strongly associated with asthma than with non-AR.<sup>27</sup> However, this association was contradicted by yet another study reporting that children with AR and those with non-AR had similar risks of developing asthma.<sup>28</sup> In our present study, the cluster with high atopy and impaired lung function (cluster 3) had significantly higher prevalences of BHR at the time of enrollment and newly developed BHR and asthma symptoms during follow-up. A positive BHR test result alone cannot be interpreted as a confirmed asthma diagnosis. Nevertheless, our findings revealed that one, not all, of the rhinitis clusters had a high initial BHR rate that was associated with significantly higher rates of new BHR and asthma symptoms, indicating that our cluster analysis identified at least one allergic march–associated rhinitis phenotype.

The underlying pathophysiologic mechanism of both AR and BHR involves bidirectional interactions between the nose and bronchi.<sup>8,29</sup> Accordingly, the treatment of rhinitis might have affected the natural course of illness among children in clusters 2 and 3, including the likelihood of subsequent development of asthma. To date, several studies sought to identify determinants of BHR in participants with AR exhibiting no clinical evidence of asthma.<sup>25,30,31</sup> Although sensitization to specific allergens, such as *D. farinae*, cat dander, and grass pollen, and the number of positive skin responses has been associated with an increased risk of BHR, the results were inconclusive.<sup>25,31</sup> In the present study, we found that cluster 3, which had a high rate of atopy and impaired lung function, also had a significantly higher rate of sensitization to multiple allergens than the clusters with a lower rate of atopy or normal lung function (data not shown). This finding suggested that school-aged children with a high atopic burden and impaired lung function were more likely to develop allergic march than those with other phenotypes.

Compared with the control group, the prevalence of newly developed BHR was lower in cluster 1, which was characterized by high prevalences of nonatopy and low socioeconomic status. Because atopy is closely correlated with BHR,<sup>32</sup> the higher prevalence of atopy in combination with its interactions with other factors might be associated with the higher prevalence of newly developed BHR in the control group than that in cluster 1 during the prospective follow-up period. Cluster 2, which was characterized by high prevalences of atopy and normal lung function, had a slightly lower prevalence of newly developed asthma symptoms than that of cluster 3 during the prospective follow-up period, although this finding was not statistically significant. The control group had a 17% rate of atopy and accounted for 5.1% of children with newly developed asthma symptoms during the prospective follow-up period. Considering the higher prevalence of atopy along with impaired lung function in cluster 3, we speculate that specific factors affecting lung function might play a role in newly diagnosed asthma in children with rhinitis. Further studies elucidating these issues are warranted.

In the present study, we also determined whether rhinitis clusters were associated with specific risk factors, including those related to microbial exposure, such as pet ownership, family size, daycare attendance, and antibiotic use in early life; all of these factors affect immune system regulation.<sup>33</sup> Although none of the abovementioned risk factors were found to be associated with the rhinitis clusters (data not shown), we observed that the socioeconomic statuses of clusters were significantly different, as reflected by the household income and level of maternal education. Although the association between socioeconomic status and childhood rhinitis remains controversial,<sup>24</sup> socioeconomic status

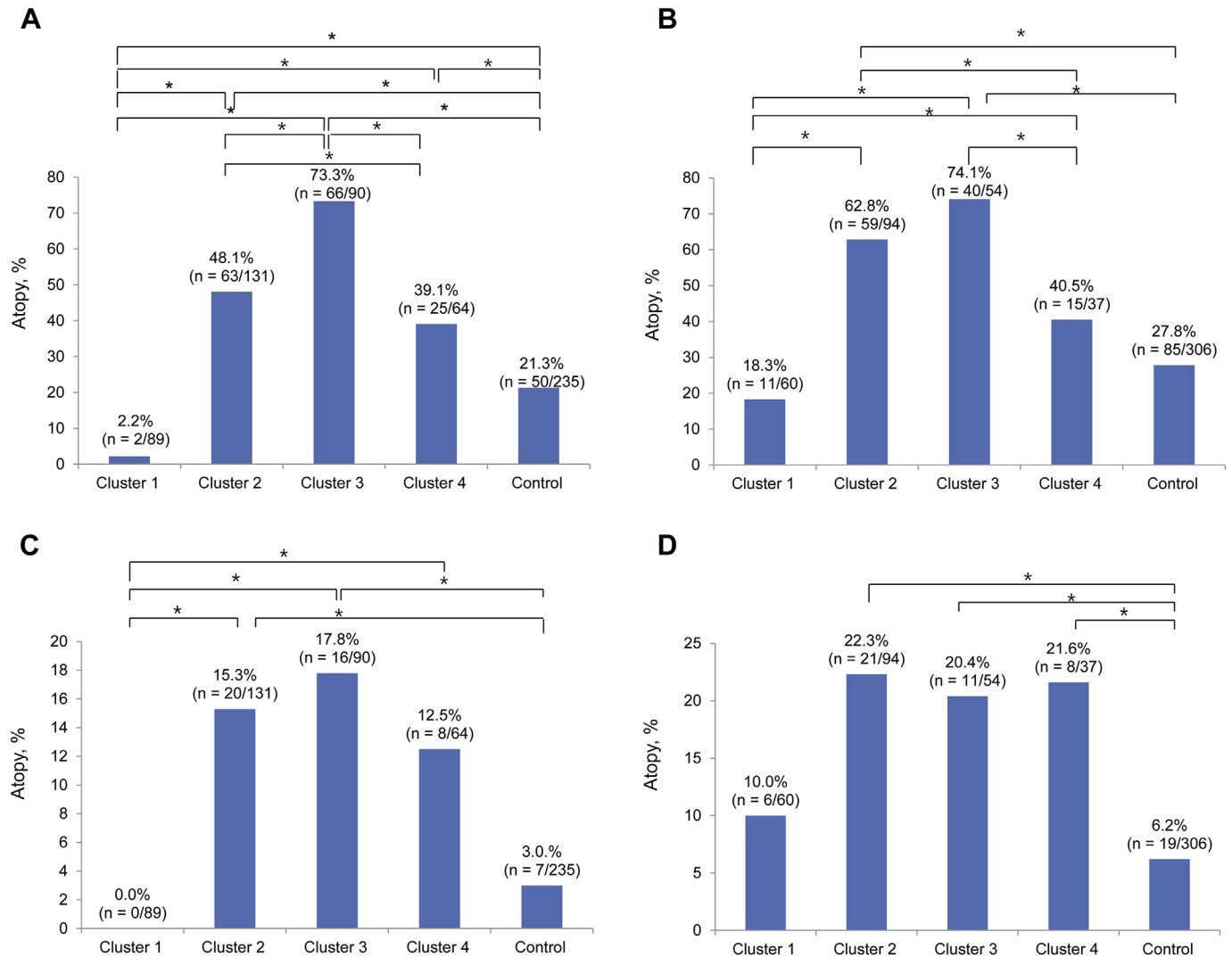


**Figure 2.** Prevalence of atopy indicating sensitization to 1 or more indoor allergens at enrollment (A) and follow-up (B). Prevalence of atopy indicating sensitization to 1 or more outdoor allergens at enrollment (C) and follow-up (D). Indoor allergens included *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, dog dander, cat epithelium, and cockroach. Outdoor allergens were grass pollen mixture, tree mixture, ragweed, mugwort, alder, oak, *Alternaria alternate*, and *Aspergillus fumigatus*. \* $P < .001$  using the  $\chi^2$  test. There were no significant differences unless indicated.

was previously suggested to affect the development of allergic diseases.<sup>34</sup> This effect of socioeconomic status might reflect differences in lifestyle, including diet, use of air purifiers, response to stress, dwelling type, and hospital accessibility, along with complex interactions among these associated factors. In this study, the income and educational levels had a weak correlation ( $r = 0.273$ ,  $P < .001$ ). To date, most studies have focused on the effect of socioeconomic status on the development of allergic diseases, including AR.<sup>24,35</sup> Our findings suggest that children with rhinitis could be classified according to socioeconomic status, which had distinct effects on rhinitis phenotypes. Additional detailed studies are needed to elucidate the effects of socioeconomic status on the development of rhinitis and underlying mechanisms.

It is critical to have a good understanding of the overlap among rhinitis phenotypes that were not clearly delineated between clusters, as observed here and in previous reports.<sup>20,36</sup> This overlap might indicate a shared common immunopathophysiologic mechanism among the 4 clusters identified in this study. Further studies are needed to improve the characterization and identification of differences among the clusters, with the ultimate goal of developing tailored and more effective treatments for specific

clusters. The first step toward achieving this goal is to obtain an integrated and comprehensive understanding of the heterogeneity of rhinitis.

Our present study was a prospective, general population–based study; thus, its findings can be generalized to school-aged children. However, this study has several limitations. First, the study was based on a questionnaire that lacked items to assess the severity and frequency of the main symptoms of rhinitis; these factors might be critical for rhinitis classification.<sup>36</sup> Second, rhinitis could not be classified into perennial and seasonal types because of the lack of relevant information included in the questionnaire. Instead, rhinitis was classified based on the SPT results. Although sensitization to specific allergens does not correspond to the induction of rhinitis symptoms,<sup>37</sup> we found that the 4 rhinitis clusters in this study had significantly different prevalence of sensitization to indoor allergens, suggesting that sensitization to specific allergens results in disparate pathophysiologic mechanisms underlying the 4 rhinitis clusters. Unfortunately, nasal cytologic testing, which could provide additional data to aid in assessing underlying pathophysiologic differences observed among the rhinitis clusters, was not performed.

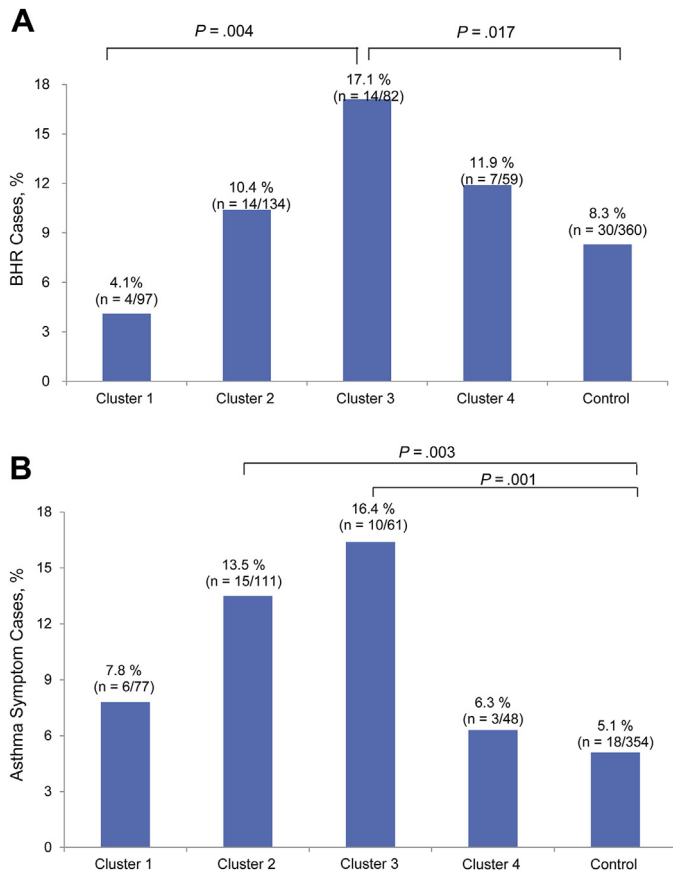


**Figure 3.** Development of new cases with bronchial hyperresponsiveness (A) and asthma symptoms (B) in each rhinitis cluster and in the control group during the prospective follow-up period. There were no significant differences unless indicated.

In summary, we identified 4 rhinitis clusters in school-aged children based on environmental and  $T_H2$  immunity-related factors, including blood eosinophil percentage, total serum IgE levels, and degree of atopy in this prospective study. Increased prevalence of atopy and impaired lung function at the time of enrollment were strongly associated with the new development of BHR in the ensuing 4-year follow-up period. The findings of this study suggested that classification of rhinitis had defined clusters, one of which was more strongly associated with the development of BHR and asthma. Our results also suggested that this strong association is partially attributable to a link between the upper and lower airways. The identification of an allergic march-associated rhinitis phenotype and investigations of risk factors for this cluster will allow for the prediction of prognoses and development of personalized medicine. The results of this study will aid physicians in identifying rhinitis subgroups that require specific treatments and in preventing asthma and BHR development by aggressive treatment in high-risk patients with rhinitis. These findings will also guide scientists in elucidating the underlying pathophysiologic mechanisms of rhinitis subgroups, providing future opportunities for the development of biomarkers associated with early diagnosis and prognosis in patients with rhinitis at high risk for asthma and BHR.

#### Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.04.016>.

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**eTable 1**Comparison of Demographic and Clinical Characteristics of the Study Cohort<sup>a</sup>

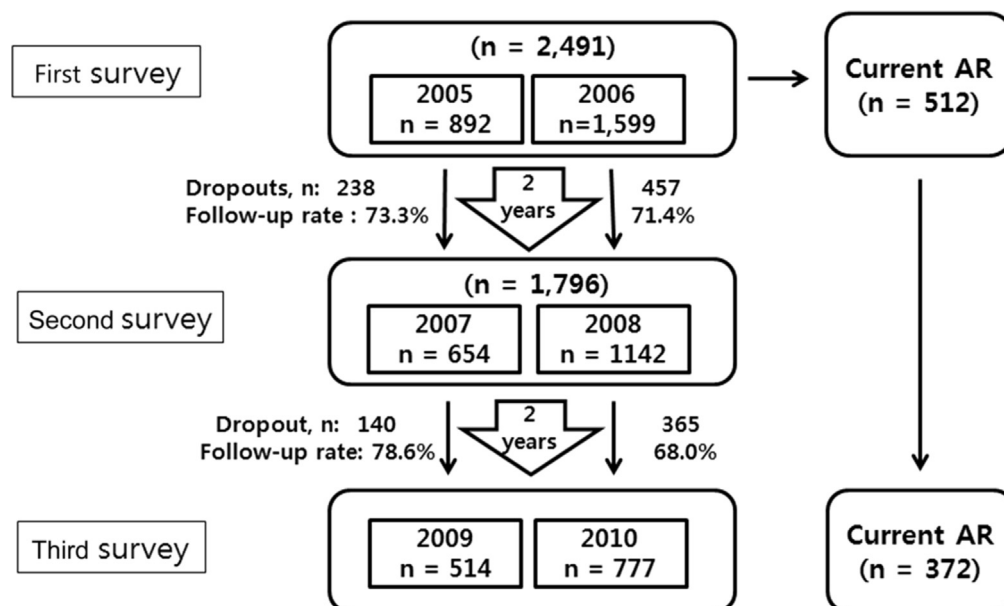
| Variables                                                          | Children With Current Rhinitis (n = 512) | Included <sup>b</sup> (n = 882) | Children Without Current Rhinitis (n = 1,979) | P Value <sup>c</sup> |
|--------------------------------------------------------------------|------------------------------------------|---------------------------------|-----------------------------------------------|----------------------|
| Age, mean (SD), y                                                  | 7.5 (0.9)                                | 7.5 (0.8)                       | 7.7 (1.2)                                     | .91                  |
| Sex                                                                |                                          |                                 |                                               | .002                 |
| Male                                                               | 298 (58.2)                               | 464 (52.6)                      | 999 (50.5)                                    |                      |
| Female                                                             | 214 (41.8)                               | 418 (47.4)                      | 980 (49.5)                                    |                      |
| BMI, mean (SD)                                                     | 16.7 (2.4)                               | 16.7 (2.4)                      | 16.9 (2.6)                                    | .14                  |
| Parental history of any allergic diseases (AD, AR, or asthma), yes | 234/495 (47.3)                           | 328/861 (38.1)                  | 445/1,846 (24.1)                              | <.001                |
| Monthly household income, US\$                                     |                                          |                                 |                                               | <.001                |
| <3,000                                                             | 320/506 (63.2)                           | 589/874 (67.4)                  | 1,333/1,856 (71.8)                            |                      |
| ≥3,000                                                             | 186/506 (36.8)                           | 285/874 (32.6)                  | 523/1,856 (28.2)                              |                      |
| Positive skin test result at the first survey                      | 205/512 (40.0)                           | 220/609 (36.1)                  | 482/1,976 (24.4)                              | <.001                |
| Methacholine PC <sub>20</sub> ≤8 mg/mL at the first survey         | 116/498 (23.3)                           | 175/859 (20.4)                  | 372/1,927 (19.3)                              | .048                 |
| Log total serum IgE at the first survey, mean (range), kU/L        | 5.0 (1.2–8.5)                            | 4.7 (0.88–8.5)                  | 4.5 (0.3–8.8)                                 | <.001                |
| Eosinophils at the first survey, mean (range), %                   | 4.39 (0.2–39.1)                          | 3.87 (0.0–39.1)                 | 3.48 (0–22.6)                                 | <.001                |

Abbreviations: AR, allergic rhinitis; AD, atopic dermatitis; BMI, body mass index; PC<sub>20</sub>, the concentration of methacholine needed to produce a 20% reduction in forced expiratory volume in 1 second from baseline.

<sup>a</sup>Data are presented as number (percentage) unless otherwise indicated.

<sup>b</sup>The included group indicates the 4 rhinitis phenotype clusters and the control group.

<sup>c</sup>Comparison between children currently with rhinitis and those without rhinitis using the  $\chi^2$  test or *t* test, as appropriate.

**eFigure 1.** Flowchart of the present study as a part of the Children's Health and Environment Research study. AR indicates allergic rhinitis.