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Association of Polysensitization, Allergic Multimorbidity, and Allergy Severity: A Cross-Sectional Study of School Children

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Key Words

Allergic multimorbidity · Polysensitization · Disease severity · Asthma · Rhinitis · Atopic dermatitis · Conjunctivitis · Food allergy

Abstract

Background: Aeroallergen sensitization is related to the coexistence of allergic diseases, but the nature of this relationship is poorly understood. The aim of this study was to clarify the relationship of polysensitization with allergic multimorbidities and the severity of allergic diseases. ***Methods:*** This study is a cross-sectional analysis of 3,368 Korean children aged 6–7 years-old. We defined IgE-mediated allergic diseases based on structured questionnaires, and classified the sensitivity to 18 aeroallergens by logistic regression and the Ward hierarchical clustering method. The relationship of polysensitization (positive IgE responses against 2 or more aeroallergens classes) with allergic multimorbidities (coexistence of 2 or more of the following allergic diseases: asthma, rhinitis, eczema, and conjunctivitis) and severity of allergic diseases was determined by ordinal logistic regression analysis. ***Results:*** The rate of polysensitization was 13.6% (n = 458, 95% CI 12.4–14.8) and that of allergic multimorbidity was 23.5% (n = 790, 95% CI 22.0–24.9). Children sensitized to more aeroallergens tended to have more allergic diseases (rho = 0.248, $p < 0.001$), although the agreement between polysensitization and multimorbidity was poor (kappa = 0.11, $p < 0.001$). The number allergen classes to which a child was sensitized increased the risk of wheezing attacks (1 allergen: adjusted odds ratio [aOR] 2.22, 4 or more allergens: aOR 9.39), absence from school (1 allergen: aOR 1.96, 3 allergens: aOR 2.08), and severity of nasal symptoms (1 allergen: aOR 1.61, 4 or more allergens: aOR 4.38). ***Conclusion:*** Polysensitization was weakly related to multimorbidity. However, the number of allergens to which a child is sensitized is related to the severity of IgE-mediated symptoms.

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Introduction

Allergy is a common chronic disease in children, and affected individuals usually have allergic multimorbidity, which is the coexistence of 2 or more allergic diseases. The prevalence of allergic multimorbidity is more common than expected due to genetics [1] or based on shared or nonshared environmental exposures [2]. Previous research examined the prevalence and sequential progression of allergic comorbidities (asthma, rhinitis, and eczema) [3, 4], and recommended that these should not be regarded as separate diseases [2].

There is a strong association between IgE sensitization and allergic diseases [1, 5], but the attributable risk is only 30–50% [2, 6, 7]. The presence, severity, and number of factors associated with IgE sensitization are important indicators for diagnosing [8–10] and predicting the progression of allergic diseases [11]. In contrast to monosensitization, polysensitization is associated with distinct clinical and immunologic reactivities [12–15]. However, the relationship between the number of allergens to which an individual is sensitized and IgE-mediated allergic disease is unclear. Previous studies have examined the relationship of polysensitization with disease severity [16] and quality of life [17], but a review of this topic reported conflicting results [18, 19]. Moreover, these studies examined a single allergic disease and did not consider allergic multimorbidity.

The aims of this study of children from Korea were to estimate the overall prevalence and relationship between aeroallergen sensitization and IgE-mediated allergic multimorbidity (asthma, rhinitis, eczema, conjunctivitis, and food allergy) and the influence of polysensitization on disease severity. Thus, we determined the patterns of polysensitization for 18 aeroallergens in 6- to 7-year-old children by use of linear regression analysis and a hierarchical clustering algorithm. We hypothesized that polysensitization is related to allergic multimorbidity and the severity of allergic diseases.

Methods

Study Design and Population

The prevalence of sensitization was determined by skin prick testing in Korean children (6–7 years old) between October and November 2010. The full details of the study were reported elsewhere [20]. In brief, this nationwide cohort study screened 3,615 children within the given age range and ultimately enrolled 3,368 (93.2%) subjects. Children in whom a skin prick test was not performed or who did not answer the questionnaire were excluded from the final analysis. All participants were tested for sensitivity to 18 aeroallergens [21]. Standardized questionnaires based on the International Study on Allergies and Asthma (ISAAC) [22] were completed by the parents, and information on family history of allergic disease was collected. Body mass index (BMI) z-scores (kg/m^2), modified for the Korean population, were calculated [23]. The study design and protocol were approved by a central institutional review board. Written consent was obtained from the parents or guardians of all children.

Definition of Allergic Disease

We examined the most common IgE-mediated allergic diseases in children, namely asthma, rhinitis, eczema, and conjunctivitis [22], and determined their presence using the ISAAC questionnaire. We diagnosed conjunctivitis by asking the parents: "Did your child have a problem with itching eyes when he/she did not have viral-induced conjunctivitis." If the answer was affirmative, we asked: "In the past 12 months, has your child had a problem with itching eyes when he/she did not have viral induced conjunctivitis." Allergic multimorbidity was defined as the coexistence of at least 2 of asthma, rhinitis, eczema, and conjunctivitis [24]. The control group consisted of children who did not have asthma or any other allergic disease.

Sensitization to Aeroallergens

Allergic sensitization to the following 18 aeroallergens was determined (Allergopharma, Reinbeck, Germany): 3 mites, cockroach, dog dander, cat dander, 4 tree pollens, 3 grass pollens, 3 weed pollens, and 2 mold allergens [21]. To classify subjects as having non-, mono-, or polysensitization, a logistic regression analysis was performed for patients who were sensitized to more than 2 allergens, followed by adjustment for sex [25]. To identify phenotypes within diverse skin data sets, we used a hierarchical clustering algorithm with the Ward minimum-variance method, which was previously used to identify distinct allergy phenotypes [26]. At each generation of clusters, the Ward method joined the clusters, meaning within-cluster variation was minimized [26].

Definition of Sensitization and Allergic Disease

Allergic sensitization was investigated by skin prick tests, with a positive result defined as a wheal diameter of more than 3 mm. The severity of asthma-related discomfort was determined by the answers to the following 4 questions. "How many attacks of wheezing has your child had in the last 12 months?" The response was coded as 0 (none), 1 (1–3 attacks), or 2 (≥4 attacks). "In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?" The response was coded as 0 (never), 1 (less than 1 night per week), or 2 (1 or more nights per week). "In the last 12 months, has wheezing ever been severe enough to limit your child's speech to one or two words at a time between breaths?" The response was coded as 0 (no) or 1 (yes). "How many days of the academic year has your child missed school due to dyspnea with wheezing, whistling, or severe cough?" The response was coded as 0 (none), 1 (1–3 days), 2 (4–6 days), or 3 (>6 days).

The severity of rhinitis was classified by the answer to the following question: "In the past 12 months, how much did your child's nose problems interfere with his/her daily activities?" The response was coded as 0 (not at all), 1 (a little bit), 2 (a moderate amount), or 3 (a lot).

The severity of eczema was classified by the answer to the following question: "In the past 12 months, how often, on average,

Table 1. Characteristics of all 3,368 subjects: children with no allergic disease and children with 1 or more allergic diseases

Characteristic	No allergic disease (n = 1,438, 42.7%)	Allergic disease(s) (n = 1,930, 57.3%)	p value
Male, n (%)	687 (47.8)	1,056 (53.6)	**0.001**
Age, years (SD)	7.0 (0.2)	7.0 (0.2)	0.948
Allergic disease, n (%)			
Asthma	–	317 (9.4)	
Rhinitis	–	1,457 (43.3)	
Eczema	–	616 (18.3)	
Conjunctivitis	–	597 (17.7)	
Parental history of allergy, n (%)			
Asthma	42 (2.9)	117 (6.1)	**<0.001**
Rhinitis	496 (34.5)	1,070 (55.4)	**<0.001**
Eczema	102 (7.1)	250 (13.0)	**<0.001**
BMI, z-score (SD)	−0.16 (1.22)	−0.15 (1.20)	0.922
Sensitization, n (%)	449 (31.2)	962 (49.8)	**<0.001**
Total IgE (SD)	1.79 (0.64)	2.07 (0.70)	**<0.001**
TEC, % (SD)	3.15 (2.37)	4.80 (3.80)	**<0.001**

Sensitization is defined as a positive reaction to at least 1 aeroallergen. Total IgE numbers are $\log_{10}$-transformed values. Significant p values are in bold. BMI, body mass index; IgE, immunoglobulin E; TEC, total eosinophil count.

has your child been kept awake at night by an itchy rash?" The response was coded as 0 (never), 1 (less than 1 night per week), or 2 (1 or more nights per week).

Statistical Analysis

The prevalence of an allergic disease was expressed as a percentage and the 95% confidence interval (CI). The χ^2 test was used to evaluate differences in dichotomous variables, and the Student t test to evaluate differences in continuous variables. We used analysis of variance (ANOVA) with least square difference in post hoc analysis to compare the group mean values. Comparisons that employed the χ^2 test used the Bonferroni correction because 3 categories were compared (nonsensitization, monosensitization, and polysensitization, i.e. no allergic disease, single allergic disease, and 2 or more coexisting allergic diseases).

The kappa coefficient was utilized to compare the level of agreement between aeroallergen sensitization (nonsensitized, monosensitized, and polysensitized) and the number of allergic diseases (none, 1, 2, or more). The significance of the kappa coefficient and differences in proportions were determined by 95% CIs.

For the dependent variables in disease severity with 2 response categories (such as speech difficulty), logistic regression analyses was used; for the dependent variables with 3 or more response categories (such as wheezing attack, sleep disturbance, school absence in asthma, and severity of rhinitis and eczema) ordinal logistic regression was conducted; for the dependent variables with food allergy, regular linear regression analyses were performed to determine whether polysensitization was associated with the severity of allergic disease.

The influence of possible confounding variables (sex, BMI, and parental asthma, rhinitis, and eczema) was investigated by adding the factors as covariates to the regression models. Adjusted odds ratios (aORs) and 95% CIs were then calculated. In the ordinal logistic regression, the data did not meet the proportional odds assumption (score test, $p < 0.01$). A 2-sided p value <0.05 was considered significant for all estimates. Statistical analyses were performed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows and ordinary regression analysis with SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

The study population consisted of 3,368 Korean children who were 6–7 years of age (mean ± SD 6.97 ± 0.16). There were no significant differences in sex, age, and family history of allergy among the enrolled children and the 247 children who were excluded. Among all enrolled children, 1,930 (57.3%) had at least 1 allergic disease. Table 1 shows the demographic characteristics of the study population. A higher percentage of children with an allergic disease were male (47.8 vs. 53.6%, $p = 0.001$). Relative to children with no allergic disease, those with allergic disease(s) had significantly greater aeroallergen sensitization (31.2 vs. 49.8%), geometric mean total IgE (1.79 kU/L

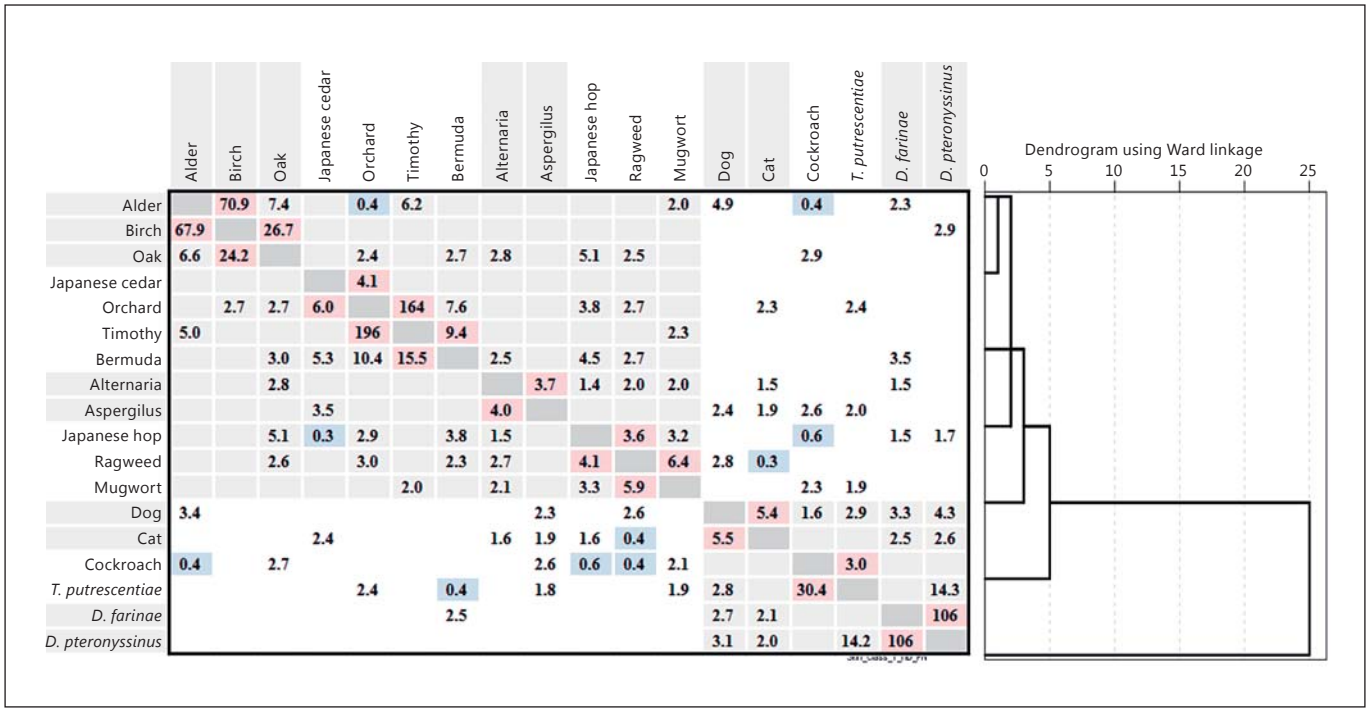

Fig. 1. ORs (left) and cluster analysis (right) of 18 aeroallergens. We classified the 18 aeroallergens into 7 groups: (1) house dust mites (*D. pteronyssinus* and *D. farinae*); (2) cockroach and *T. putrescentiae*; (3) pets (cat and dog); (4) weed pollens (mugwort, ragweed, and Japanese hop); (5) molds (*A. alternata* and *A. fumigatus*); (6) grass pollens (orchard, timothy, and Bermuda) and Japanese cedar, and (7) tree pollens (alder, birch, and oak). Each group was classified as an indoor allergen (large red box, lower right; groups 1, 2, and 3) or outdoor allergen (large blue box, upper left; groups 4, 5, 6, and 7). The number inside each small box indicates the age- and sex-adjusted OR of sensitization, with pink shadows indicating a significant positive relationship and blue shadows indicating a significant negative relationship. For example, 70.9 is the aOR of sensitization to birch for subjects sensitized to alder, and 67.9 is the aOR of sensitization to alder for subjects sensitized to birch. A box was left blank when the relationship between the allergens was statistically insignificant. The right panel is a dendrogram in which clusters were identified using the Ward hierarchical clustering method.

vs. 2.07 kU/L), mean total eosinophils (3.15 vs. 4.80%), and family history of allergy (all comparisons: $p < 0.001$).

Classification of Aeroallergen Sensitization

Figure 1 shows the odds ratios (ORs, left) of the relationships of the different allergens and cluster analysis (right) of the 18 allergens. On the left, the number inside each square indicates the OR calculated by regression analysis. For example, patients sensitized to alder were very likely to be sensitized to birch (OR 70.9). Only statistically significant ORs are given; an OR in a red or white/gray square indicates a positive relationship, and an OR in a blue square indicates a negative relationship.

The left part of Figure 1 is a dendrogram based on Ward linkage that categorizes the 18 aeroallergens into 7 classes. This analysis identifies 7 different classes of aeroallergens as: tree (alder, birch, and oak), grass (Japanese cedar, orchard, timothy, and Bermuda), mold (*Alternaria alternata* and *Aspergillus fumigatus*), weed (Japanese hop, ragweed, and mugwort), animal (dog and cat), cockroach (cockroach and *Tyrophagus putrescentiae*), and house dust mite (*Dermatophagoides farinae* and *D. pteronyssinus*). Japanese cedar was classified as a grass rather than a tree and *T. putrescentiae* was placed in the same class as cockroaches instead of mites, as shown in Figure 1. We grouped indoor allergens in a large red rectangle (lower right), and outdoor allergens in a large blue rectangle (upper left).

Relationship of Polysensitization with Multimorbidity

Table 2 compares the characteristics of children who were sensitized to different numbers of allergens. Among all 3,368 children, 1,987 (59.0%) were nonsensitized, 381 (41.0%) were sensitized to 1 allergen, and 458 (13.6%)

Table 2. Characteristics of all 3,368 subjects stratified by allergic sensitization status

Characteristic	Nonsensitized (n = 1,987, 59.0%)	Monosensitized (n = 923, 27.4%)	Polysensitized (n = 458, 13.6%)	p value
Participants, n (%)				**<0.001**
Control	958 (49.0)	328 (34.4)[a]	109 (23.8)[a,b]	
Allergic	999 (51.0)	625 (65.6)	349 (76.2)	
Age, years (SD)	6.98 (0.15)	6.97 (0.18)	6.98 (0.14)	0.219
Sex, n (%)				**<0.001**
Male	936 (47.8)	497 (54.2)[a]	269 (58.7)[a]	
Female	1,021 (52.2)	436 (45.8)	189 (41.3)	
Obesity, n (%)[1]	60 (3.8)	24 (3.1)	12 (3.2)	0.243
Total IgE ≥100, n (%)[2]	566 (29.8)	619 (67.1)[a]	374 (82.7)[a,b]	**<0.001**
TEC >4%, n (%)[3]	290 (15.2)	454 (48.6)[a]	283 (62.9)[a,b]	**<0.001**
Family history, n (%)				
Parental asthma	79 (4.0)	55 (5.8)	25 (5.5)	0.085
Parental AR	854 (43.6)	499 (52.4)[a]	213 (46.5)	**<0.001**
Parental AD	187 (9.6)	118 (12.4)	47 (10.3)	0.064

AR, allergic rhinitis; AD, atopic dermatitis; TEC, total eosinophil count; IgE, immunoglobulin E. Obesity was defined by a BMI z score greater than 2. Significant p values are in bold. [a] Significantly different from the nonsensitization group (χ^2 test with Bonferroni correction). [b] Significantly different from the monosensitization group (χ^2 test with Bonferroni correction).

[1] n = 2,710. [2] n = 3,295. [3] n = 3,289.

were sensitized to 2 or more allergens (polysensitization). There were 968 (49.5%) children with an allergic disease in the nonsensitization group and 616 (64.6%) in the monosensitization group. Compared to those who were nonsensitized, mono- and polysensitization were more common among males ($p < 0.001$), children with an allergic disease ($p < 0.001$), and children with a parental history of rhinitis ($p < 0.001$). In addition, children who were monosensitized and polysensitized had statistically significant differences in total IgE and total eosinophil counts (all comparisons: $p < 0.001$).

There were 1,140 (33.9%) children with a single allergic disease, and 790 (23.5%) with 2 or more IgE-mediated allergic diseases (2 diseases: n = 566, 16.8%; more than 2 diseases: n = 224, 6.7%). There were also positive relationships between the number of allergic diseases and male sex, total IgE, total eosinophil count, parental asthma, rhinitis, and atopic dermatitis (Table 3). The kappa score for the presence and absence of sensitization and allergic disease was 0.18 (95% CI 0.15–0.21, $p < 0.001$), which was lower than we predicted, despite the similarity of the 2 conditions. The kappa score was even lower when the children were classified into 3 separate groups (non-, mono-, polysensitization vs. none, single, multimorbidity; kappa = 0.11, 95% CI 0.09–0.14, $p < 0.001$).

Figure 2 shows the percentages of patients who had different numbers of allergic diseases (0–4, in different shades of grey) according to the number of allergens to which they were sensitized (none to 4 or more). This figure shows that as the number of allergens to which children were sensitized increased from 0 to 4 or more, the percentage of children with no allergic disease decreased from 50.5 to 5.7%. Moreover, 94.3% of children who were sensitized to 4 or more allergens had at least 1 allergic disease. Linear regression analysis indicated that the number of positive skin reactions correlated with the risk of allergic disease ($p < 0.001$).

Figure 3 shows the results of ordinal regression analyses of the number aeroallergens to which children were sensitized (abscissa) with allergic multimorbidity (aORs and 95% CIs), with adjustment for confounding. This figure shows that the aOR for allergic multimorbidity was greater for children who were sensitized to more allergens (1 allergen: aOR 1.82, 95% CI 1.54–2.14, $p < 0.001$; 2 allergens: aOR 2.67, 95% CI 2.10–3.41, $p < 0.001$; 3 allergens: aOR 4.10, 95% CI 2.63–6.40, $p < 0.001$; 4 or more allergens: aOR 5.31, 95% CI 2.60–10.84, $p < 0.001$).

Relationship of Polysensitization with Asthma Severity

Table 4 shows the results of the ordinal regression analysis of the relationship of polysensitization with asth-

Table 3. Characteristics of study subjects with 1 or multiple allergic diseases

Characteristic	1 disease (n = 1,140, 33.9%)	Allergic multimorbidity (n = 790, 23.5%)			
		2 diseases (n = 566, 16.8%)	3 diseases (n = 181, 5.4%)	4 diseases (n = 43, 1.3%)	p value
Nonsensitized, %	57.3	44.0	32.0	18.6	**<0.001**
Sensitized, %	42.7	56.0	68.0	81.4	**<0.001**
Age, years (SD)	6.98 (0.15)	6.97 (0.16)	6.96 (0.19)	6.98 (0.15)	0.652
Sex, %					**0.031**
Male	51.7	54.2	60.8	67.4	
Female	48.3	45.8	39.2	32.6	
Obesity, %	5.4	6.1	2.2	5.6	0.366
Total IgE ≥100, %	49.0	61.2	72.7	85.4	**<0.001**
TEC >4%, %	32.9	45.9	58.2	75.0	**<0.001**
Family history, %					
Parental asthma	4.2	6.9	11.6	20.9	**<0.001**
Parental AR	51.9	58.5	63.5	74.4	**<0.001**
Parental AD	11.3	13.6	17.1	30.2	**<0.001**

AR, allergic rhinitis; AD, atopic dermatitis; IgE, immunoglobulin E; TEC, total eosinophil count. Obesity was defined by a BMI z score greater than 2. The statistical significance of differences of sensitization, sex, obesity, and family allergic history were analyzed by a χ^2 test with a linear association. Significant p values are in bold.

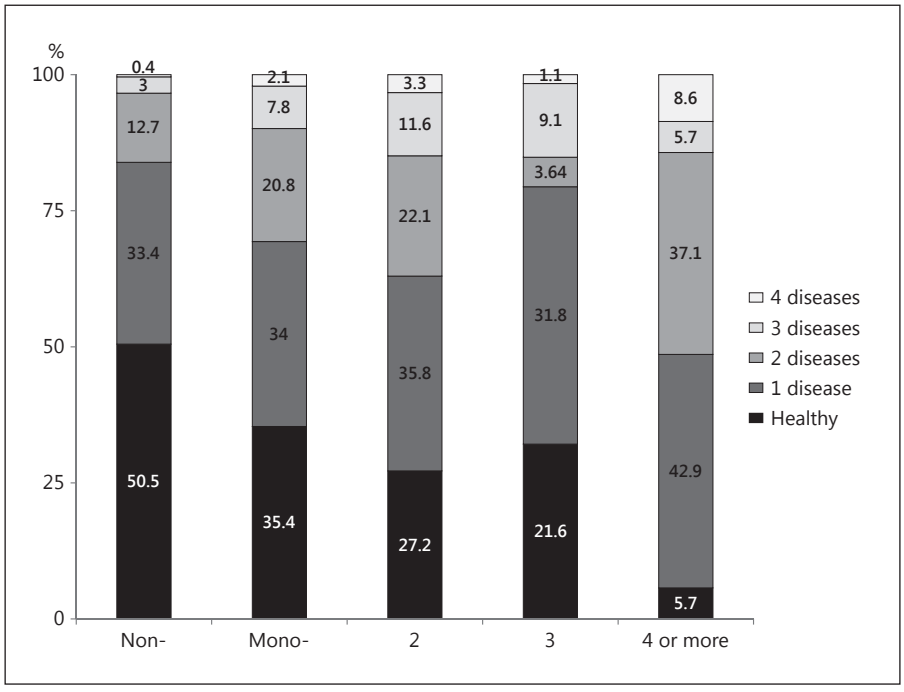

Fig. 2. Relationship of the number aeroallergens to which an individual is sensitized (abscissa; 0, 1, 2, 3, 4, or more) with the number of allergic diseases (ordinate; 0, 1, 2, 3, or 4).

ma severity. The number of allergens to which children are sensitized was significantly associated with the number of wheezing attacks within the last 12 months (2 allergens: aOR 2.75, 95% CI 1.02–7.38, p = 0.044; 3 allergens: aOR 5.91, 95% CI 1.39–25.12, p = 0.016; 4 or more allergens: aOR 9.39, 95% CI 1.70–51.96, p = 0.010). It was also significantly related with the number of days of school absence. However, polysensitization had no significant effect on sleep disturbance and speech difficulty due to asthma.

Table 4. Ordinal logistic regression analysis of the effects of polysensitization on asthma

Allergen sensitizations	Asthma symptom							
	wheezing attacks		sleep disturbance		speech difficulty		school absence	
	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
0	(ref.)	–	(ref.)	–	(ref.)	–	(ref.)	–
1	2.22 (0.99–4.99)	0.053	1.11 (0.75–1.64)	0.614	0.97 (0.42–2.23)	0.994	1.96 (1.47–2.61)	**<0.001**
2	2.75 (1.02–7.38)	**0.044**	1.60 (0.96–2.67)	0.071	0.58 (0.16–2.16)	0.418	2.51 (1.67–3.76)	**<0.001**
3	5.91 (1.39–25.12)	**0.016**	2.09 (0.84–5.21)	0.115	0.94 (0.10–8.48)	0.958	2.08 (1.05–4.12)	**0.036**
4 or more	9.39 (1.70–51.96)	**0.010**	0.37 (0.072–1.94)	0.242	4.29 (0.68–27.10)	0.122	2.48 (0.97–6.36)	0.058

The regression analysis controlled for the following confounding factors: sex, parental asthma, rhinitis, atopic dermatitis, and BMI. The severity of each asthma symptom was scored as described in Methods. Significant *p* values are in bold.

Relationship of Polysensitization with Rhinitis and Eczema

Table 5 shows the results of the ordinal regression analysis of the relationship of polysensitization with severity of rhinitis and frequency of night awakening due to eczema. The severity of nasal symptoms was significantly greater in children who were mono- or polysensitized (1 allergen: aOR 1.61, 95% CI 1.34–1.94, $p < 0.001$; 2 allergens: aOR 1.98, 95% CI 1.51–2.60, $p < 0.001$; 3 allergens: aOR 2.67, 95% CI 1.64–4.36, $p = 0.037$; 4 or more allergens: aOR 4.38, 95% CI 1.80–10.70, $p = 0.001$). Night awakening due to eczema was significantly more likely in children sensitized to 2 aeroallergens (aOR 1.95, 95% CI 1.43–2.65, $p < 0.001$).

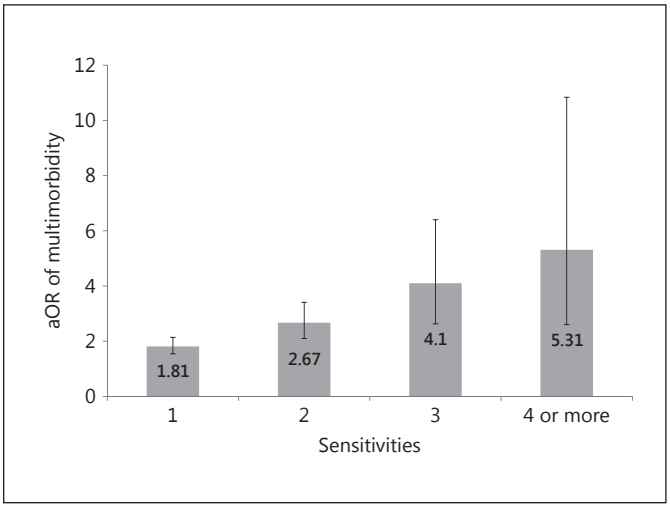

Fig. 3. Relationship of the number of aeroallergens to which an individual is sensitized (abscissa) with allergic multimorbidity (aOR with 95% CIs), with adjustment for confounding by sex, BMI, parental asthma/atopic dermatitis, and total eosinophil/IgE values.

Discussion

Main Findings

Our study showed that 13.6% of the children had polysensitization and 23.5% had allergic multimorbidities. The number of allergic diseases and aeroallergens to which children were sensitized were positively related. A total of 94.3% of children who were sensitized to 4 or more aeroallergens had at least 1 allergic disease, which is 5.31-fold more than among the controls. However, there was a poor agreement between the number of allergens to which a child is sensitized and the number of allergic diseases. After adjusting for confounding factors, we found that polysensitization was significantly associated with the frequency of asthma attacks, days of school absence, and extent of nasal discomfort. This study also found distinct associations of allergic multimorbidity with high IgE levels, total eosinophil count, parental allergic rhinitis, and male sex, and that polysensitization was related to allergic multimorbidity. To our knowledge, this is the first study of allergic multimorbidities that evaluated the association of the severity of allergic diseases with the number of aeroallergens to which an individual is sensitized.

Co- and Cross-Sensitization

We classified the 18 assayed aeroallergens into 7 groups by calculating a dendrogram and by logistic regression analysis. Our analysis classified storage mite with cockroach, and Japanese cedar with grasses, unlike the classic

Table 5. Ordinal logistic regression analysis of the effects of polysensitization on rhinitis and eczema

Allergen sensitizations	Nasal symptoms		Eczema symptoms	
	aOR (95% CI)	*p* value	aOR (95% CI)	*p* value
0	(ref.)	–	(ref.)	–
1	1.61 (1.34–1.94)	**<0.001**	1.24 (0.98–1.56)	0.069
2	1.98 (1.51–2.60)	**<0.001**	1.95 (1.43–2.65)	**<0.001**
3	2.67 (1.64–4.36)	**<0.001**	1.49 (0.84–2.64)	0.174
4 or more	4.38 (1.80–10.70)	**0.001**	2.12 (0.88–5.10)	0.092

The regression analysis controlled for the following confounding factors: sex, parental asthma, allergic rhinitis, atopic dermatitis, and BMI. The severity of nasal and eczema symptoms were scored as described in Methods. Significant *p* values are in bold.

classification [14], although all other groups had the typical classifications. This discordance may result from the presence of certain allergenic molecules, such as polcalcin, which is a panallergen for timothy (Phl p 7) and Japanese cedar (Jun o 4), and exhibits serologic cross-sensitization. Cross reactivity among *tyr* and *bla* is not yet well defined, although there is evidence for cross-reactivity of mites and cockroaches [10]. This may also be related to the high rate of sensitization to Japanese cedar in Jeju-do, located in southern Korea, where sensitization to grass is high, thereby increasing the risk of cosensitization due to the overlapping environment exposures. Our comprehensive aeroallergen tests classified the allergens systemically, which is in contrast to previous studies that examined cosensitization. Sensitization differs according to the specific allergic disease [27], but we found that the extent and type of sensitization to indoor allergens were closely associated with asthma, in contrast to outdoor allergens. This finding is consistent with a previous study [28]. However, we found that this difference between indoor and outdoor allergens did not occur for the other 3 allergic diseases.

Prevalence of Polysensitization and Multimorbidity

The prevalence of polysensitization in the present study was 13.6%. This is similar to previous reviews, which reported polysensitization of 10–22% in adults [10, 29] and 10–22% in children [7, 30]. Few studies have estimated the prevalence of allergic multimorbidity, but it was 23.5% in our population. There are several reports of allergic multimorbidities in individuals with asthma [31, 32], allergic rhinitis [33, 34], and eczema [35] because such identification is essential for monitoring and treating allergic diseases. However, studies of allergic multimorbidities in childhood are scarce [32], and there is no comprehensive data on the prevalence of allergic multimorbidities in children.

Relationship between Polysensitization and Multimorbidity

Polysensitization has distinct biological correlates, such as high total IgE and eosinophil levels [13, 14], male sex [7, 14], and parenteral allergic diseases [14]. Allergic multimorbidity and polysensitization seem to have the same risk factors [36]. However, we found that the agreement between allergic multimorbidity and polysensitization was poor. This discordance could be because allergic diseases share common causal mechanisms with allergen-specific IgE (30–50%) [2, 6, 7], nonallergic mechanisms [1], and other factors, such as non-IgE mechanisms and the environment [2, 36], which contribute to the development of allergic multimorbidity. Allergic multimorbidity has distinct clinical phenotypes compared to single diseases [10, 14, 37].

A previous study reported a relationship between the number of allergens to which an individual is sensitized and the type and number of allergic diseases [7]. In particular, an examination of the association between the number of coexisting allergic diseases and sensitization in 981 children with allergic disorders indicated that 80% of the children who were sensitized to 4 or more allergens had asthma, eczema, and/or rhinitis [7]. In our study, 94.3% of the children had 1 or more allergic diseases, which is higher than in previous reports.

Disease Severity and Sensitization

Despite the recent focus on the clustering of aeroallergens that have similar sensitization effects in children [1,

5], the association of allergic disease severity with polysensitization remains relatively understudied [16, 34, 38]. Polysensitization is significantly associated with a poor quality of life in patients with allergic rhinitis [17] and intermittent asthma [19], and with higher asthmatic symptom scores for dyspnea, wheezing, and cough [13]. Moreover, impaired lung function occurs in polysensitized patients with allergic rhinitis [39]. These previous findings correspond well with our results.

Why does polysensitization increase the risk for disease severity? The reason for this association is unclear, but it might be related to the increased duration of exposure, frequency of exposure, and extent of inflammation in polysensitized individuals. Furthermore, polysensitized children may have a defective production of IL-10 and IFN-γ [40], as well as bronchial impairment [39]. These findings support the hypothesis that polysensitization is a distinct clinical entity and that the underlying immunological alterations could be responsible for the development of more severe allergic diseases such as asthma.

Strengths and Limitations

The strengths of the current study include the large sample size, the comprehensive use of IgE testing, use of stringent statistics for the classification of different aeroallergen classes, use of validated questionnaires, and the nationwide coverage of a specific age group of children. This study also assessed the clinical significance of IgE and total eosinophil count, which are considered important in studies of allergic sensitization and diseases. However, this study has some potential limitations. The cross-sectional design prevents us from making conclusions regarding cause-and-effect. The questionnaires utilized for conjunctivitis were not verified, although we used the ISAAC questionnaire for asthma, allergic rhinitis, and atopic dermatitis. The diagnosis and disease-related discomfort were measured by symptom-based questionnaires, and this could have led to misclassification because we did not consider other allergic diseases, such as urticaria, drug allergy, and anaphylaxis. Finally, we identified polysensitization by responses to different allergen extracts, because polysensitization reflects exposures in the same environment, rather than molecular and/or structural differences in allergens [1].

Conclusions

The current study confirmed the general features of polysensitization and the relationship between polysensitization and allergic multimorbidity. Polysensitization is also related to asthma severity, as indicated by the frequency of wheezing events, days of school absence, and severity of allergic rhinitis. Despite these findings, the consistency of the relationship of polysensitization with multimorbidity was lower than we predicted. Children with allergic multimorbidity have similar clinical features as those who are polysensitized. The results of this study provide a general overview of the association of allergic multimorbidity, polysensitization, and severity of 4 allergic diseases.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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