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Original Article

Association of Sensitization to Different Aeroallergens With Airway Function and Nasal Patency in Urban Children

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ABSTRACT

Purpose: Children with sensitization to aeroallergens have decreased lung function and nasal patency. Our purpose was to determine the association of sensitization to different aeroallergens with airway function and nasal patency.
Methods: Four hundred and eighty-six randomly selected 11 year-old children who lived in Seongnam City were examined. Serum specific immunoglobulin E (IgE) levels against 6 common allergens (*Dermatophagoidesfarinae*, birch, cat, dog, Japanese hop and *Alternaria*), impulse oscillometry (IOS) results for the evaluation of airway dysfunction, and acoustic rhinometry for the determination of nasal airway patency were obtained.
Results: IOS indicated that children sensitized to *Alternaria* (n = 38, 7.8%) and dog dander (n = 69, 14.2%) had decreased lung function, based on resistance at 10 Hz (Rrs10; aβ = 0.0072; 95% CI, 0.017, 0.127; $P = 0.010$) and 1 Hz (Rrs1; aβ = 0.038; 95% CI, 0.001, 0.074; $P = 0.042$). Children sensitized to *D. farinae* (n = 281, 57.8%) had decreased post-decongestant nasal volume at 0 to 5 cm (aβ = −0.605; 95% CI, −1.005, −0.205; $P = 0.003$), but normal IOS results at all measured frequencies ($P > 0.05$). Increased serum eosinophil level was associated with Rrs1 ($P = 0.007$) and Rrs2 ($P = 0.018$) and post-decongestant nasal volume at 0 to 5 cm (aβ = −0.885; 95% CI, −1.331, −0.439; $P < 0.001$).
Conclusions: Sensitivity to specific aeroallergens, serum eosinophil count and total IgE level had different associations with upper and lower airway dysfunction in urban children.

Keywords: Lung function tests; oscillometry; rhinometry; allergens; eosinophil count

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INTRODUCTION

There are well-established associations of sensitization to aeroallergens with asthma and allergic rhinitis (AR) in children.[1,2] Studies that documented increased bronchial hyper-responsiveness[3] and decreased nasal volume[4] in aeroallergen-sensitized individuals support this relationship. However, only a limited number of studies have suggested a relationship of specific allergen sensitization patterns with clinical outcomes.[2,5,6] Because asthma and AR are heterogeneous conditions, the presence of aeroallergen sensitization in the upper or lower airways must be considered for the clinical management of these conditions. For example, sensitization to pollen is associated with AR,[6,7] sensitization to fungi is associated with the severity[8] and development of asthma,[9,10] and sensitization to animal dander is associated with asthma[5,7] and bronchial hyper-responsiveness.[3] However, no comprehensive investigation that used quantitative examinations, such as impulse oscillometry (IOS) or acoustic rhinometry, has yet examined the relationships of sensitization to different aeroallergens with upper and lower airway diseases.

We hypothesized that the site-specific effect of sensitization to different aeroallergens impacts the clinical manifestations of asthma and AR. Therefore, we examined the sensitization to aeroallergens and their effects on upper and lower airways by measuring nasal volume using acoustic rhinometry and airway dysfunction using IOS. We also examined the association of serum eosinophil count and total immunoglobulin E (IgE) level with nasal volume change and small airway dysfunction.

MATERIALS AND METHODS

Subject enrollment

This prospective, general population-based and cross-sectional study was part of the Seongnam Atopy Project for Children's Happiness (SAP_{2017}) program, which was sponsored by the Seongnam City Government for the prevention and education of allergic diseases in Korean children. The SAP_{2017} was performed at 11 elementary schools in Seongnam City (Gyeonggi Province, Republic of Korea) between March and August of 2017. The study subjects were 620 urban children who were 10 to 12 years-old.

Questionnaires

The Korean version of the International Study of Asthma and Allergies in Childhood study was used to determine the presence of allergic disease (asthma and AR), based on symptoms during the previous 12 months. Pet owners were those who answered "yes" to the question, "Do you have any pets in your household living with your child?" and were asked to identify the type of pet. Individuals who were exposed to 'visual mold' were those who answered "yes" to the question, "Do you see any wet moldy spots on the ceilings or walls in your household?" Individuals who were exposed to 'smelling mold' were those who answered "yes" to the question, "Do you smell mold in your household?"

Blood sampling

Serum total and allergen-specific IgE levels to 6 common aeroallergens in Korean children[11] (*D.farinae*, dog dander, cat dander, birch, Japanese hop and *Alternaria*) were measured using the ImmunoCAP system (Phadia AB, Uppsala, Sweden). A serum allergen-specific IgE level of 0.35 kU/L or more was defined as positive. As some studies have suggested IgE level of

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0.7 kU/L as positive, we have analyzed our data with both cutoff values and acquired similar results. Subjects with no positive results were considered non-sensitized, those with 1 positive result mono-sensitized, and those with 2 or more positive results poly-sensitized. The percentage of blood eosinophils was calculated, and serum total IgE was measured using a fluorescent enzyme-linked immunosorbent assay (ImmunoCAP system, Phadia AB).

Determination of airway dysfunction using IOS

Airway dysfunction was measured using the Jaeger MasterScreen IOS system (Jaeger Company, Wurtzburg, Germany).[12] The signal duration was 30 seconds or longer, and measurements of 3 acceptable maneuvers were acquired at each time while monitoring flow curves. Airway resistance was measured at 1 Hz (Rrs1), Rrs2, Rrs3, Rrs5, Rrs10, Rrs15 and Rrs20. Rrs20-5 was calculated as the difference of Rrs5 and Rrs20.

Determination of nasal patency using acoustic rhinometry

Nasal patency was measured using the A1 Acoustic Rhinometer (GM Instruments Ltd, Kilwinning, UK), according to standardized international recommendations.[13] A well-trained technician applied the probe to each subject's nostrils and asked the subject to hold his/her breath for approximately 5 seconds. Both nasal cavities were decongested by administering a single puff of intranasal xylometazoline (1 mg/mL), and rested for 15 minutes before volume measurement. The post-decongestant nasal patency characterized by measuring the volume (cm^3) at 0 to 5 cm behind the nostril opening (vol 0–5 cm), the volume (cm^3) at 2 to 5 cm behind the nostril opening (vol 2–5 cm), and the minimal cross-sectional area (MCA; cm^2) of the nasal cavity. For quality control, measurements were repeated at least 3 times until the standard deviation was less than 15%.

Fractional exhaled nitric oxide (FeNO) measurements

FeNO (in parts per billion [ppb]) was measured using the Niox-mino (Aerocrine AB,Solna, Sweden) according to American Thoracic Society/European Respiratory Society recommendations.[14] Each subject was seated in a comfortable position, took a full inhalation and then exhaled at a constant flow rate.

Statistical analysis

All analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA) and R Packages (version 3.5.0; R Foundation, Vienna, Austria). The primary outcome measures were the associations of small airway dysfunction (from IOS) and nasal patency (from acoustic rhinometry) with sensitization to 6 different aeroallergens. The secondary outcome measures were the associations of IOS and acoustic rhinometry data with total eosinophil count (TEC), total IgE level and FeNO level. To analyze the association of airway dysfunction with sensitization and of nasal volume with sensitization, Student's *t*-test was used for continuous variables and the χ^2 test was used for categorical variables. All IOS results were adjusted for height, sex and body mass index (BMI) z-score and additional covariates that could affect small airway lung function based on previous studies. This analysis adjusted for all variables that affected the estimate by more than 10%. For IOS data, the odd ratios (ORs) for the relationship of resistance at 1, 2, 3, 5, 10, 15 and 20 Hz with categorical variables in the aero-allergen test, FeNO (20 ppb), TEC (4%) and total IgE (150 kU/L) were determined using generalized linear regression with a logit function.

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Ethics statement

The study protocol was approved by the Institutional Review Board (IRB) of CHA Bundang Medical Center (IRB No. 2017-04-049). Written informed consent was obtained from the parents or guardians of all participants following a detailed explanation of the study.

RESULTS

Characteristics of the subjects

A total of 620 subjects completed the questionnaire, and serum specific-IgE data were available for 486 (78.4%) children (**Table 1**). The median age was 11.0 years, 50.4% of the subjects were male, 34.8% were not sensitized to any of the 6 aeroallergens, 34.2% were monosensitized, and 31.1% were polysensitized.

Factors affecting small airway lung function and nasal patency

We obtained IOS data and nasal patency data for 469 (96.5%) children, and performed regression analysis to identify factors significantly associated with airway dysfunction and nasal patency. Age and height affected airway resistance at all frequencies tested, and BMI affected resistance at frequencies of 5 Hz and above. Moreover, airway resistance at 1 and 5 Hz was significantly greater for males than for females (**Supplementary Tables S1** and **S2**). Nasal volume was also strongly associated with height and age, and MCA had a strong relationship with BMI z-score (**Supplementary Table S3**).

Prevalence of allergic diseases and allergen sensitization

A total of 281 (57.8%) children were sensitized to *D. farinae*, and fewer children were sensitized to birch (n = 110, 22.6%), cat dander (n = 80, 16.5%), dog dander (n = 69, 14.2%), Japanese hop and *Alternaria* (**Table 2**). The prevalence of asthma was low (n = 10, 2.1%) and was associated with sensitization to *D. farinae* (0.5% vs. 3.3%, $P = 0.032$), dog dander (0.7% vs. 10.4%, $P < 0.001$) and *Alternaria* (1.6% vs. 7.9%, $P = 0.030$). After adjustment for confounding factors, sensitization to dog dander (adjusted OR [aOR], 17.080) and *Alternaria* (aOR, 5.661) remained associated with asthma.

The prevalence of AR was greater in children with sensitization to each of the aeroallergens tested except Japanese hop (**Table 2**). After adjustment for confounding factors, sensitization to *D. farinae* (aOR, 1.979; 95% CI, 1.340, 2.923; $P = 0.001$), cat dander (aOR, 1.751; 95% CI, 1.021, 3.005; $P = 0.042$), and birch (aOR, 1.729; 95% CI, 1.067, 2.801; $P = 0.026$) remained associated with AR.

Association of sensitization to aeroallergens with pet ownership and mold exposure

Among the 484 children for whom data were available, there were 81 pet-owners (16.7%); 44 (9.1%) children had dogs and 12 (2.5%) had cats. More dog owners than non-owners were sensitized to dog dander (47.7% vs. 10.7%, $P < 0.001$), but cat ownership was not associated with sensitization to cat dander ($P = 0.410$). There were no significant associations of *Alternaria* sensitization with visual exposure to mold ($P = 0.577$) or smelling of mold ($P = 0.975$).

Association of airway dysfunction with aeroallergen sensitization

Airway dysfunction in children who were sensitized or not sensitized to 6 aeroallergens was determined by measuring resistance at 1, 2, 3, 5, 10 and 20 Hz, with adjustment for

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Table 1. Demographic and clinical characteristics of the children enrolled (n = 486)

Variable	No.* (%)
Sex	
Boy	245 (50.4)
Girl	241 (49.6)
Age (yr)	11.0 ± 0.89
Height (cm)	149.5 ± 7.9
BMI (kg/m^2)	
Obesity	31 (6.4)
Overweight	49 (10.1)
Normal	377 (77.6)
Underweight	29 (6.0)
Asthma (n = 479)	
No	469 (97.9)
Yes	10 (2.1)
AR (n = 482)	
No	206 (42.7)
Yes	276 (57.3)
Aero-allergen sensitization (n = 486)	
D. Farinae	256 (53.1)
Dog	56 (11.5)
Cat	73 (15.0)
Birch	86 (17.7)
Japanese hop	32 (6.6)
Alternaria	35 (7.2)
FeNO (n = 477)	
High (35 ≥ ppb)	34 (7.1)
Low (35 < ppb)	443 (92.9)
Total IgE (N = 486)	
High 150 kU/L ≤	190 (39.1)
Low 150 kU/L >	296 (60.9)
Blood eosinophils (n = 472)	
High 4% ≤	137 (29.0)
Low 4% >	335 (71.0)
IOS (n = 469)	
Rrs1 (hPa/L/s)	7.19 (1.19)†
Rrs2 (hPa/L/s)	6.56 (1.20)†
Rrs3(hPa/L/s)	5.93 (1.21)†
Rrs5 (hPa/L/s)	4.94 (1.23)†
Rrs10(hPa/L/s)	3.88 (1.20)†
Rrs15 (hPa/L/s)	3.20 (1.23)†
Rrs20 (hPa/L/s)	3.16 (1.21)†
Nasal decongestant test	
Vol 0–5 cm	11.0 (2.27)
Vol 2–5 cm	8.32 (1.93)
MCA	1.32 (0.59)

Values are reported as mean ± SD or number (%).
SD, standard deviation; BMI, body mass index; Obesity, BMI z-score more than 2 SDs above the mean; overweight, 1 to 2 SDs above the mean; underweight, more than 2 SDs below the mean; AR, allergic rhinitis; FeNO, fraction of exhaled nitric oxide; IgE, immunoglobulin E; IOS, impulse oscillometry system; Rr, resistance of respiratory system; vol 0–5 cm, nasal volume (cm^3) at 0 to 5 cm behind the nostril opening; vol 2–5 cm, nasal volume (cm^3) at 2 to 5 cm behind the nostril opening; MCA, minimal cross-sectional area (cm^2) of the nasal cavity.
*Number with available data. Among the 480 children who performed acoustic rhinometry, 16 MCA and 32 decongestant test results were incomplete and excluded from analysis; †Geometric means with geometric SD.

confounding factors (height, BMI z-score, gender, passive smoking and prematurity or low birth weight) (**Figure**). The Rrs values had no significant associations with sensitization to *D. farinae* (**Figure A**), cat (**Figure B**), birch (**Figure D**) or Japanese hop (**Figure E**). However, Rrs10 (aβ = 0.072; 95% CI, 0.017, 0.127; *P* = 0.010), Rrs15 (aβ = 0.101; 95% CI, 0.034, 0.168; *P* = 0.003) and Rrs20 (aβ = 0.084; 95% CI, 0.025, 0.144) were significantly lower in children sensitized to *Alternaria* (**Figure D**), although there was no significant association of Rrs 20-5

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Table 2. Association of acoustic rhinometry results with aeroallergen sensitization status

Variables	MCA				Vol 0–5 cm			
	β (95% CI)	*P* value	aβ (95% CI)	*P* value	β (95% CI)	*P* value	Adjusted (95% CI)	*P* value
Sensitization								
Non	Ref		Ref		Ref		Ref	
Mono-	−0.119 (−0.203 ,−0.034)	0.006	−0.109 (−0.193, −0.024)	0.012	−0.047 (−0.091, −0.003)	0.035	−0.046 (−0.089, −0.004)	0.034
Poly-	−0.137 (−0.228 ,−0.047)	0.003	−0.129 (−0.221, −0.038)	0.006	−0.059 (−0.105, −0.013)	0.012	−0.059 (−0.104, −0.013)	0.011
Total IgE								
< 150	Ref		Ref		Ref		Ref	
> 150	0.035 (−0.034, 0.104)	0.320	−0.121 (−0.234, −0.008)	0.036	−0.357 (−0.774, 0.060)	0.093	−0.432 (−0.840, −0.024)	0.038
Eosinophil								
< 4%	Ref		Ref		Ref		Ref	
> 4%	−0.102 (−0.176, −0.028)	0.007	−0.202 (−0.325, −0.079)	0.001	−0.990 (−1.437, −0.544)	< 0.001	−0.885 (−1.331, −0.439)	< 0.001
D. farinae								
No	Ref		Ref		Ref		Ref	
Yes	−0.100 (−0.173, −0.027)	0.007	−0.091 (−0.164, −0.018)	0.015	−0.044 (−0.082, −0.007)	0.020	−0.038 (−0.086, 0.010)	0.117
Birch								
No	Ref		Ref		Ref		Ref	
Yes	−0.112 (−0.211, −0.014)	0.025	−0.100 (−0.200, 0.000)	0.049	−0.043 (−0.091, 0.006)	0.088	−0.038 (−0.086, 0.010)	0.117
Cat								
No	Ref		Ref		Ref		Ref	
Yes	−0.024 (−0.128, −0.079)	0.649	−0.021 (−0.124, 0.082)	0.688	−0.013 (−0.065, 0.040)	0.637	−0.011 (−0.062, 0.040)	0.675
Dog								
No	Ref		Ref		Ref		Ref	
Yes	0.015 (−0.103, 0.133)	0.801	0.011 (−0.105, 0.128)	0.848	−0.021 (−0.079, 0.037)	0.480	−0.016 (−0.072, 0.041)	0.583
Japanese hop								
No	Ref		Ref		Ref		Ref	
Yes	-	-	−0.002 (−0.157, 0.154)	0.983	0.044 (−0.031, 0.119)	0.251	0.035 (−0.038, 0.107)	0.352
Alternaria								
No	Ref		Ref		Ref		Ref	
Yes	−0.107 (−0.244, 0.030)	0.126	−0.092 (−0.228, 0.044)	0.186	−0.057 (−0.129, 0.015)	0.120	−0.056 (−0.125, 0.014)	0.118

Data were adjusted for height, sex and BMI z-score, and were analyzed using gamma-generalized linear regression. Independent variables: coefficients in regression analysis of sensitization status adjusted for sex, height and BMI; dependent variables: nasal decongestant test results.
IgE, immunoglobulin E; CI, confidence interval;vol 0–5 cm, nasal volume at 0 to 5 cm behind the nostril opening; MCA, minimal cross-sectional area of the nasal cavity.

with *Alternaria* sensitization (aβ = −0.061; 95% CI, −0.183, 0.061; *P* = 0.328). Sensitization to dog dander was associated with Rrs1 (aβ = 0.038, 95% CI, 0.001, 0.074; *P* = 0.042) and Rrs2 (aβ = 0.037; 95% CI, 0.000, 0.074; *P* = 0.051), but not with resistance at any higher frequencies. The number of sensitized aeroallergens (mono- or poly-sensitization) was not associated with airway dysfunction at Rrs 1, 5 and 20 (*P* > 0.05 for Rrs1, 5 and 20).

Association of nasal patency with aeroallergen sensitization

Analysis of the relationship of nasal patency (vol 0–5 cm, vol 2–5cm and MCA) with allergen sensitization indicated that MCA and vol 0–5 cm were significantly decreased in children who were mono- and poly-sensitized (**Table 3**). In addition, MCA and vol 0–5 cm were significantly decreased in children who were sensitized to *D. farinae* (MCA: aβ = −0.154; 95% CI, −0.264, −0.011; *P* = 0.006 and vol 0–5 cm: aβ = −0.605; 95% CI, −1.005, −0.205; *P* = 0.003), but not with any of the other aeroallergens tested. Vol 0–5 cm was also decreased in cat owners relative to non-owners

Association of serum eosinophil count with total IgE level

Analysis of serum eosinophil level as a continuous variable indicated it had a significant association with Rrs1 (aβ = 0.040; 95% CI, 0.011, 0.069; *P* = 0.007). There was no association of total IgE level with sensitization status (non-, mono- or poly-sensitization) or airway resistance. Cat or dog ownership and visual mold or smelling mold had no significant associations with the IOS results. After adjusting for confounding factors, a serum eosinophil

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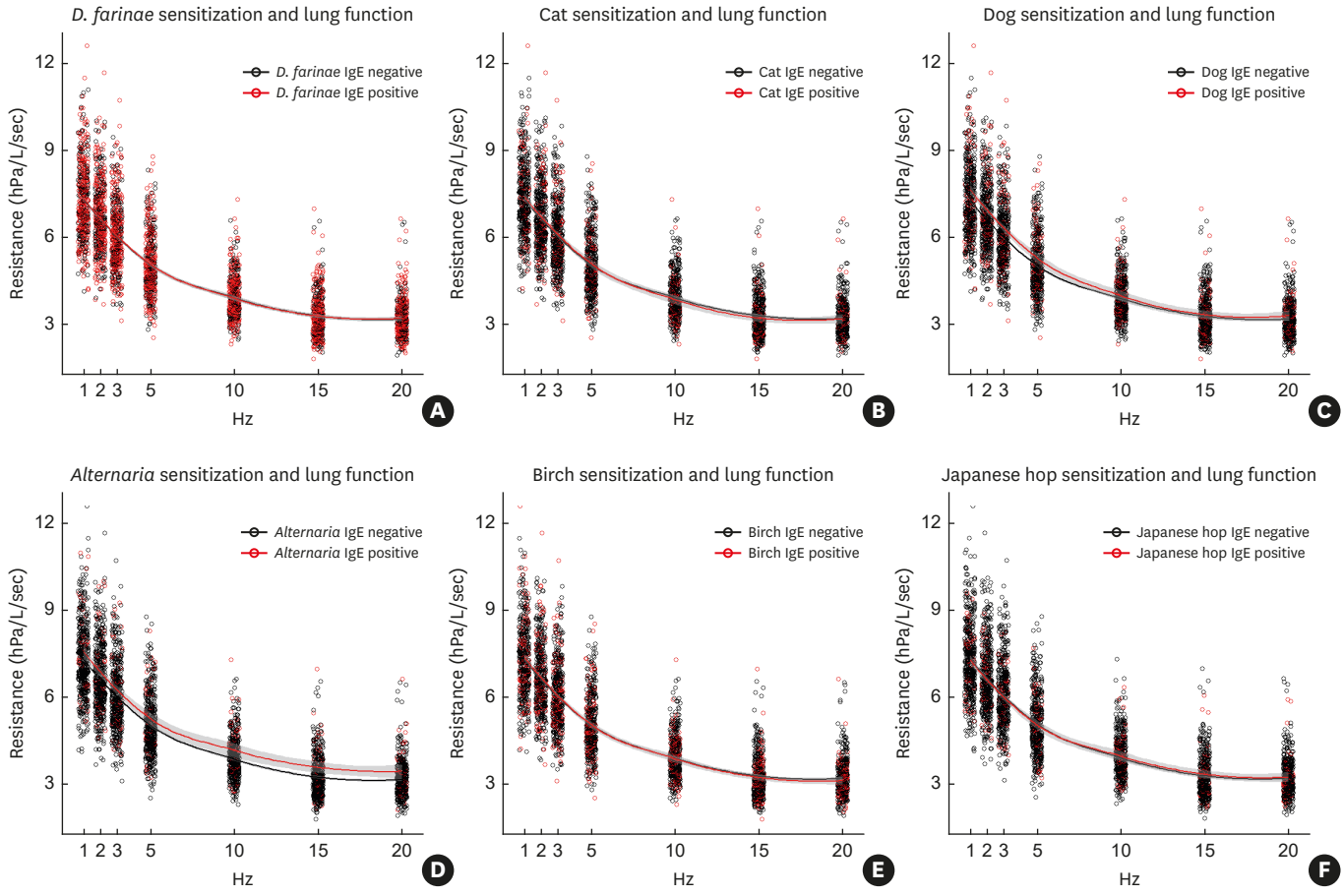

Figure. Locally weighted scatterplot smoothing of impulse oscillometry resistance at 1, 2, 3, 5, 10, 15 and 20 Hz for 6 aeroallergens. Shaded areas indicate 80% confidence intervals. Sensitization to *Alternaria* (D) was significantly associated with Rrs10, Rrs15, and Rrs20 and sensitization to Dog (C) was significantly associated with Rrs1. Sensitization to *D. farinae* (A), Cat (B), Birch (E) and Japanese hop (F) were not significantly associated with small airway dysfunction at any tested frequency.
IgE, immunoglobulin E.

Table 3. Association of aeroallergen sensitization status with airway resistance at different frequencies

Hz	Dependent variable								
	Total IgE		TEC		Sensitization				
					Non-	Mono-		Poly-	
	aβ (95% CI)	*P* value	aβ (95% CI)	*P* value	Ref	aβ (95% CI)	*P* value	aβ (95% CI)	*P* value
Rrs1	0.008 (−0.019, 0.034)	0.578	**0.040 (0.011, 0.069)**	**0.007**	-	0.013 (−0.017, 0.043)	0.410	0.029 (−0.003, 0.061)	0.075
Rrs2	0.007 (−0.020, 0.034)	0.592	**0.036 (0.006, 0.066)**	**0.018**	-	0.017 (−0.013, 0.048)	0.264	0.027 (−0.005, 0.060)	0.097
Rrs3	0.007 (−0.022, 0.036)	0.636	0.031 (−0.001, 0.063)	0.061	-	0.023 (−0.010, 0.057)	0.174	0.026 (−0.010, 0.061)	0.153
Rrs5	0.005 (−0.028, 0.037)	0.768	0.023 (−0.013, 0.059)	0.209	-	0.025 (−0.012, 0.062)	0.191	0.022 (−0.017, 0.062)	0.269
Rrs10	0.000 (−0.031, 0.031)	0.983	0.010 (−0.024, 0.044)	0.576	-	0.016 (−0.020, 0.052)	0.383	0.016 (−0.022, 0.053)	0.412
Rrs15	−0.002 (−0.039, 0.036)	0.933	−0.014 (−0.055, 0.028)	0.523	-	0.018 (−0.025, 0.062)	0.413	0.014 (−0.032, 0.060)	0.556
Rrs20	−0.007 (−0.041, 0.027)	0.680	−0.009 (−0.046, 0.028)	0.628	-	0.017 (−0.022, 0.055)	0.399	0.014 (−0.026, 0.055)	0.489
Rrs20-5	0.029 (−0.040, 0.097)	0.411	0.064 (−0.012, 0.140)	0.100	-	0.066 (−0.012, 0.145)	0.097	0.040 (−0.043, 0.122)	0.347

Data were adjusted for sex, height and BMI, and were analyzed using gamma-generalized linear regression. Independent variables: immune status (total IgE, TEC and sensitization); dependent variables: lung function parameters. Positive serum total IgE: ≥150 kU/L; positive serum eosinophil: ≥4%; poly-sensitization: sensitive to 2 or more of the 6 tested aeroallergens. Risk factors were sex, height, BMI z-score, prematurity or low birth weight, and exposure to secondary smoke. $P < 0.05$ is in bold.
Rr, resistance of respiratory system; IgE, immunoglobulin E; CI, confidence interval; TEC, total eosinophil count.

level above 4% was significantly associated with increased Rrs1 (aβ = 0.040; 95% CI, 0.011, 0.069; $P = 0.007$) and Rrs2 (aβ = 0.036; 95% CI, 0.006, 0.066; $P = 0.018$).

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Total IgE level was associated with decreased MCA (aβ = −0.121; 95% CI, −0.234, −0.008; $P = 0.036$) and vol 0–5 cm (aβ = −0.432; 95% CI, −0.840, −0.024; $P = 0.038$). Moreover, MCA (aβ = −0.202; 95% CI, −0.325, −0.001) and vol 0–5 cm (aβ = −0.885; 95% CI, −1.331, −0.439; $P < 0.001$) were lower in subjects with serum eosinophil levels above 4% (**Table 3**).

DISCUSSION

We found that sensitization to *Alternaria* and dog dander was associated with airway dysfunction and current asthma status, although our IOS data indicated that these allergens affected slightly different frequencies of small airway function. On the other hand, sensitization to *D. farinae* and atopic status showed that strong associations with nasal volume, and current rhinitis increased the odds ratio for sensitization to *D. farinae*, cat dander, birch and any allergen, indicating that different aeroallergens vary in their effects on the upper and the lower respiratory tracts. Our results thus suggest that strategies for the management of respiratory allergic diseases depend on the aeroallergen and on the anatomical sites affected.

A major finding of this study is that sensitization to *Alternaria* and dog dander increased airway dysfunction in this general population of children. We focused on subjects in the general population who have not been diagnosed with asthma, but have decreased lung function and aeroallergen sensitization. Adults with asthma who are sensitive to mold have more hospital admissions overall and admissions to the intensive care unit for asthma exacerbations.[8,10] In addition, sensitization to *Alternaria* is associated with airway hyper-responsiveness in non-asthmatic adults[15] and in children with mild to moderate asthma.[3] Interestingly, as in adult populations, our general pediatric population had an association of sensitization to *Alternaria* with airway dysfunction, as determined by resistance at 10 Hz, 15 Hz and 20 Hz, but not at Rrs20-5 (which represents small airway dysfunction).[16] Similarly, children with dog dander sensitization had an increased risk of current asthma and increased airway resistance. This result is consistent with those of previous studies which reported that hypersensitivity to furry animals had a strong association with asthma, although sensitization to mites, grass pollen, and cockroach were not related to asthma.[3,5,7,17] However, in contrast to our *Alternaria* results, dog dander sensitization was associated with Rrs1, implying small airway dysfunction. These findings indicate that sensitization to certain allergens plays an important role in modulating the bronchial hyper-responsiveness of children in the general population as well as in patients with asthma.

We found that sensitization to house dust mites was associated with decreased nasal volume and AR, and that sensitization to birch pollen and cat dander were associated with current AR. A genetic predisposition to allergic disease increases the risk of AR, and sensitization to pollen and/or dust mites are important determinants of AR.[6,7,18] However, we found no significant decrease in nasal decongestant volume in children sensitized to tree and weed pollen, in contrast to those sensitized to house dust mites. This could be explained by the lower concentrations and shorter durations of exposure to pollen[18] and by the unique allergenic properties of house dust mites.[19] Thus, each aeroallergen appears to elicit a site-specific allergic response in the airway due to its unique properties.

We found that airway dysfunction was not related to the presence of atopy, mono-sensitization or poly-sensitization. Thus, multiple allergic diseases can occur in children

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who are poly-sensitized to seasonal and perennial allergens, and children may be sensitized to allergens that affect the upper and lower airways. We also found an association of elevated serum eosinophil level with upper and lower airway dysfunction, in agreement with the results of previous studies which showed that increased serum eosinophil level is associated with poor lung function.[20] Serum and bronchial eosinophil levels are also related to airway obstruction[20] and more frequent hospital admissions due to asthma exacerbations.[8] However, the relationship between serum eosinophil level and upper airway function remains poorly elucidated. While there is paucity of investigation on the relationship between serum eosinophil level and upper airway function, it is noteworthy that our study demonstrated an association of elevated serum eosinophil level with upper airway dysfunction.

This study included a large number of subjects and examined the functional profiles of the upper and the lower airways. We measured the extent of site-specific airway dysfunction using the rigorous and quantitative methods of IOS and rhinometry. We did not independently examine each airway, but compared how allergens affect the upper and lower airways. Our study design had a few limitations. First of all, a selection bias may exist as we only included subjects whose parent or guardian signed an informed consent form, and it was more likely that those parent or guardian had concerns about allergic disease or their children already had allergic disease. Secondly, the nature of cross-sectional study design imposes limitations in the analysis and interpretation of the results. To establish causality, prospective and controlled studies are needed to verify the effects of different aeroallergens on the upper and lower airways.

In conclusion, we found that different aeroallergens had different effects on the upper and the lower airways of inner-city children in Korea. The presence of atopy had a strong association with nasal patency, and serum eosinophil count was associated with dysfunction of the upper and lower airways. Our results have implications for clinicians in analyzing the meaning of aeroallergen sensitization in relation to clinical presentation.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1

Identification of continuous factors that could potentially confound analysis of small airway dysfunction

Click here to view

Supplementary Table S2

Identification of binary factors that could potentially confound analysis of small airway dysfunction

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Supplementary Table S3

Prevalence (%) and aORs for asthma and AR in children with different aeroallergen sensitization status (n = 486)*

Click here to view

REFERENCES

1. Roberts G, Zhang H, Karmaus W, Raza A, Scott M, Matthews S, et al. Trends in cutaneous sensitization in the first 18 years of life: results from the 1989 Isle of Wight birth cohort study. Clin Exp Allergy 2012;42:1501-9.
PUBMED | CROSSREF
2. Kim HY, Shin YH, Yum HY, Jee HM, Jang SJ, Yoon JW, et al. Patterns of sensitisation to common food and inhalant allergens and allergic symptoms in pre-school children. J Paediatr Child Health 2013;49:272-7.
PUBMED | CROSSREF
3. Nelson HS, Szefler SJ, Jacobs J, Huss K, Shapiro G, Sternberg AL. The relationships among environmental allergen sensitization, allergen exposure, pulmonary function, and bronchial hyperresponsiveness in the Childhood Asthma Management Program. J Allergy Clin Immunol 1999;104:775-85.
PUBMED | CROSSREF
4. Chawes BL, Kreiner-Møller E, Bisgaard H. Objective assessments of allergic and nonallergic rhinitis in young children. Allergy 2009;64:1547-53.
PUBMED | CROSSREF
5. Schoos AM, Chawes BL, Melén E, Bergström A, Kull I, Wickman M, et al. Sensitization trajectories in childhood revealed by using a cluster analysis. J Allergy Clin Immunol 2017;140:1693-9.
PUBMED | CROSSREF
6. Krämer U, Oppermann H, Ranft U, Schäfer T, Ring J, Behrendt H. Differences in allergy trends between East and West Germany and possible explanations. Clin Exp Allergy 2010;40:289-98.
PUBMED | CROSSREF
7. Warm K, Hedman L, Lindberg A, Lötvall J, Lundbäck B, Rönmark E. Allergic sensitization is age-dependently associated with rhinitis, but less so with asthma. J Allergy Clin Immunol 2015;136:1559-1565.e2.
PUBMED | CROSSREF
8. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. BMC Pulm Med 2005;5:4.
PUBMED | CROSSREF
9. Knutsen AP, Bush RK, Demain JG, Denning DW, Dixit A, Fairs A, et al. Fungi and allergic lower respiratory tract diseases. J Allergy Clin Immunol 2012;129:280-91.
PUBMED | CROSSREF
10. 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.
PUBMED | CROSSREF
11. Ha EK, Baek JH, Lee SY, Park YM, Kim WK, Sheen YH, et al. Association of polysensitization, allergic multimorbidity, and allergy severity: a cross-sectional study of school children. Int Arch Allergy Immunol 2016;171:251-60.
PUBMED | CROSSREF
12. Sheen YH, Jee HM, Ha EK, Jang HM, Lee SJ, Lee S, et al. Impulse oscillometry and spirometry exhibit different features of lung function in bronchodilation. J Asthma 2018;55:1343-51.
PUBMED | CROSSREF
13. Clement PA, Gordts F; Standardisation Committee on Objective Assessment of the Nasal Airway, IRS, and ERS. Consensus report on acoustic rhinometry and rhinomanometry. Rhinology 2005;43:169-79.
PUBMED

14. American Thoracic Society; European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005;171:912-30.
PUBMED | CROSSREF
15. Hiranrattana A, Stern DA, Guerra S, Halonen M, Wright AL, Daines M, et al. *Alternaria* sensitisation at age 6 years is associated with subsequent airway hyper-responsiveness in non-asthmatics. Thorax 2018;73:1170-3.
PUBMED | CROSSREF
16. Karayama M, Inui N, Mori K, Kono M, Hozumi H, Suzuki Y, et al. Respiratory impedance is correlated with airway narrowing in asthma using three-dimensional computed tomography. Clin Exp Allergy 2018;48:278-87.
PUBMED | CROSSREF
17. Ingram JM, Sporik R, Rose G, Honsinger R, Chapman MD, Platts-Mills TA. Quantitative assessment of exposure to dog (Can f 1) and cat (Fel d 1) allergens: relation to sensitization and asthma among children living in Los Alamos, New Mexico. J Allergy Clin Immunol 1995;96:449-56.
PUBMED | CROSSREF
18. Katelaris CH, Lee BW, Potter PC, Maspero JF, Cingi C, Lopatin A, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. Clin Exp Allergy 2012;42:186-207.
PUBMED | CROSSREF
19. Thomas WR. Hierarchy and molecular properties of house dust mite allergens. Allergol Int 2015;64:304-11.
PUBMED | CROSSREF
20. Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. Eur Respir J 2018;51:1702536.
PUBMED | CROSSREF