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Original Article

Association between sensitized to food allergens and childhood allergic respiratory diseases in Taiwan

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KEYWORDS

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Nasal peak expiratory flow rate (nPEFR);
Lung function test;
Asthma control test (ACT)

Abstract *Background:* Sensitization to allergen has long been known to be related to childhood allergic diseases. Polysensitized children have more severe atopic diseases, whereas allergic rhinitis or asthma children with cosensitized to food and inhalant allergens were under-researched.

Objective: To realize the association between sensitization to food allergens and pediatric allergic rhinitis and asthma in Taiwan.

Methods: We included 138 participants with sensitized to allergen as assessed by serum-specific IgE. 87 of 138 participants had allergic rhinitis and 51 participants had asthma. All participants underwent a physical examination and measurement of serum total and specific IgE values. Besides, nasal peak expiratory flow rate (nPEFR) that was performed by the participants with allergic rhinitis and were requested to complete the Pediatric Rhinoconjunctivitis Quality of Life Questionnaires (PRQLQ). Lung function test and asthma control test (ACT)/child asthma control test (C-ACT) were performed by the participants with asthma.

Results: 39 of 87 allergic rhinitis participants with sensitized to food and inhalant allergens (AR food group), 48 of 87 allergic rhinitis participants with sensitized to inhalant allergen alone (AR inhalant group). The AR food group had significantly lower nPEFR values and higher total IgE values ($p < 0.05$) compared with the AR inhalant group. The AR food group had higher PRQLQ scores than the AR inhalant group. 24 of 51 asthma participants with sensitized to food and inhalant allergens (Asthma food group), 27 of 51 asthma participants with sensitized to inhalant allergen alone (Asthma inhalant group). The Asthma food group had significantly higher total IgE values ($p < 0.05$) compared with the Asthma inhalant group. The Asthma food group had lower lung function test values and asthma control test (ACT) scores than the other group.

Conclusions: Children with cosensitized to food and inhalant allergens have more severe clinical symptoms and abnormal laboratory findings. Sensitization to food allergen was more related to

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pediatric allergic rhinitis than asthma. We may need larger, longer and extended studies to confirm these findings.

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Introduction

Allergic diseases, including allergic rhinitis, asthma and eczema, are an important health problem that especially allergic rhinitis and asthma are the most common chronic childhood respiratory diseases, and their prevalence has been increasing considerably in the past few decades.^{1–4} Age, environmental factors, and inheritance play important roles in the development of allergy sensitization and allergic diseases.^{5–9} The children from different geographical regions, ages, climates may have different allergen sensitization profiles.

Sensitization to allergens has long been known to be related to childhood allergic diseases. Some atopic children show sensitization to only one allergen (mono-sensitization), while others show sensitization to more than one allergen (polysensitization) in allergy screening tests. Several studies have revealed that polysensitized children exhibit more severe atopic disease than mono-sensitized children,^{10,11} whereas children with cosensitized to food and inhalant allergen were under-researched. Some studies have demonstrated that food allergens are associated with atopic dermatitis,¹⁰ and inhalant allergens are associated with allergic respiratory diseases throughout childhood. Ronmark E et al. reported that sensitization to dog and horse were significant risk factors for asthma, while birch, horse, and timothy were significant risk factors for rhinitis in children.¹² However, there is limited information on the association between food allergens and childhood allergic respiratory diseases. Therefore, the purpose of our study was to realize the association between sensitization to food allergens and childhood asthma and allergic rhinitis. Furthermore, to evaluate clinical status of children with cosensitized to food and inhalant allergens.

Materials and methods

Participants and study design

This is a prospective case-controlled study. It was conducted at the Division of Allergy, Asthma and Rheumatology, Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan, between September 2014 and August 2016. This study was granted approval by the Institutional Review Board of Chung Shan Medical University Hospital, and a written informed consent was obtained from parents before commencing the study. The inclusion criteria for this study were as follows: 1) the age of subject between 4 and 18 years; 2) positive atopic

history, including allergic rhinitis, asthma and eczema based on personal history; and 3) positive findings to serum-specific IgE with inhalant and/or food allergens. Patients who had a history of any nasal or adenoid surgery and/or of asthma exacerbation with probable complications (e.g. atelectasis, pneumothorax) were excluded from the study.

A total of 138 participants were included in this study with sensitization to the allergens as assessed by serum-specific IgE. 87 of 138 participants had allergic rhinitis and 51 participants had asthma. All participants underwent a physical examination and measurement of serum total and specific IgE values. Besides, nasal peak expiratory flow rate (nPEFR) that was performed by the participants with allergic rhinitis and were requested to complete the Pediatric Rhinoconjunctivitis Quality of Life Questionnaires (PRQLQ). Lung function test and asthma control test (ACT)/child asthma control test (C-ACT) were performed by the participants with asthma.

Definition of allergic diseases

Allergic rhinitis was defined as the reported frequent or seasonal symptoms of nasal discharge and/or blockage and recurrent sneezing for 2 to 8 consecutive months. Asthma was defined as at least two reported episodes of wheezing or shortness of breath and had a positive results to bronchodilator test (increase of $\geq 12\%$ and ≥ 400 mL in FEV₁ after bronchodilator inhalation) within the last 6 months.

Total and specific serum immunoglobulin E

Serum samples were collected during the initial study. The serum levels of total and specific IgE were measured by ImmunoCAP (Phadia, Uppsala, Sweden). Specific IgE antibody test including inhalant allergens such as *House dust mite*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Dermatophagoides microrceras*, *Blomia tropicalis*, *Dog epithelia*, *Cat epithelia*, *Cockroaches*, *Aspergillus fumigatus*, *Candida albicans*, *Cladosporium herbarum*, *Penicillium notatum*, *Bermuda grass*, *Timothy grass* and *Ragweed* and food allergens such as Milk, Egg white, Crab, Shrimp and Codfish. ImmunoCAP values of ≥ 0.35 kU/L were considered indicative of allergic sensitization.¹³

Pediatric rhinoconjunctivitis quality of life questionnaire (PRQLQ)

The PRQLQ has 23 items in the five areas of nasal symptoms, ocular symptoms, practical problems, other symptoms, and activity limitations. Each item is scored using a 7-

point scale from 0 (no symptoms) to 6 (most serious symptoms).¹⁴ The questionnaire can be completed within five minutes by children, although younger aged children may need the help from their parents.

Nasal peak expiratory flow rate (nPEFR)

We recorded nPEFR with a Mini-Wright peak expiratory flow meter equipped with a purpose-built face mask, incorporating a good seal with the face. Subsequent to the placement of the face mask, patients were instructed to blow their noses forcefully after a deep inspiration while sitting with their mouths firmly closed. This test was performed three times and the highest value was recorded.

Lung function test

Flow–volume curves were recorded using a MasterScope spirometer (Erich Jaeger, Wurzburg, Germany). Subjects performed three technically acceptable trials, according to the American Thoracic Society/European Respiratory Society recommendations,¹⁵ and the highest values for forced vital capacity (FVC) and forced expiratory volume in one-second (FEV1) were recorded.

Asthma control test (ACT) and childhood asthma control test (C-ACT)

Children between 4 and 11 years of age completed the C-ACT questionnaire and those above 12 years of age completed the ACT questionnaire.

The C-ACT consists of seven items, addresses the previous 4 weeks and is divided into two parts. One part is filled in by the child and consists of four questions on perception of asthma control, limitation of activities, coughing and awakenings at night. Each question has four response options. The second part is filled in by the parent or caregiver and consists of three questions (daytime complaints, daytime wheezing and awakenings at night) with six response options. The sum of all scores yields the C-ACT score, ranging from 0 (poorest asthma control) to 27 (optimal asthma control). A cut-off point ≤ 19 indicates uncontrolled asthma.¹⁶

The ACT is a patient-completed questionnaire and consists of five items evaluating the preceding 4 weeks (limitation of activities, shortness of breath, awakenings at night, use of reliever medication and patient's perception of asthma control).^{17,18} Each question has five response options, resulting in scores of 1–5. The sum of all scores yields the total ACT score, ranging from 5 (poorest asthma control) to 25 (optimal asthma control). It has been validated from the age of 12 years and a score ≤ 19 indicates poorly controlled asthma.

Statistical analysis

Statistical analyses were carried out using the SPSS/PC 22.0 software (SPSS, Inc., Chicago, IL). The data are expressed as a mean $\pm$ standard deviation. Mann–Whitney U-test was used to compare the total IgE levels, PRQLQ scores, ACT scores and lung function test values (FEV1, FVC and FEV1/

FVC) between the two groups. $P \leq 0.05$ was considered to be significant.

Results

A total of 138 children were enrolled into this study and all completed the study, with a mean age of 8 years (range 4–18 years). 87 of 138 children had allergic rhinitis and 51 children had asthma. Each group was divided into two subgroups: one subgroups was cosensitized to food and inhalant allergens, another subgroups was sensitized to only inhalant allergens. There were no significant differences in the baseline demographics and health characteristics between the each two subgroups, including sex, family and personal history of allergy (allergic rhinitis, atopic dermatitis and asthma). Each food and inhalant allergens cosensitized subgroup was not statistically significant with respect to age and height compared with the inhalant allergen sensitized subgroup. However, food and inhalant allergens cosensitized subgroups had significantly low body mass index (BMI) (AR subgroup $p = 0.02$, Asthma subgroup $p = 0.019$) than the other subgroups (Table 1).

39 of 87 (44.83%) allergic rhinitis children were assigned to the food and inhalant allergens cosensitized subgroup (AR food group) and 48 (55.17%) to the inhalant allergen sensitized subgroup (AR inhalant group). The AR food group had significantly higher total IgE levels ($p = 0.02$) and lower nPEFR values ($p = 0.04$) compared with the AR inhalant group (Fig. 1) (Fig. 2). Although there were no statistically significant differences in the PRQLQ scores between the two groups, the AR food group scored higher than the AR inhalant group (Fig. 3).

24 of 51 (47.05%) asthma children were assigned to the food and inhalant allergens cosensitized subgroup (Asthma food group) and 27 (52.95%) to the inhalant allergen sensitized subgroup (Asthma inhalant group). The Asthma food group had significantly higher total IgE values ($p = 0.024$) compared with the Asthma inhalant group and it was also higher than the AR food group (Fig. 1). The Asthma food group had lower lung function test values and asthma control test (ACT) scores than the Asthma inhalant group (Fig. 4) (Fig. 5) (Fig. 6).

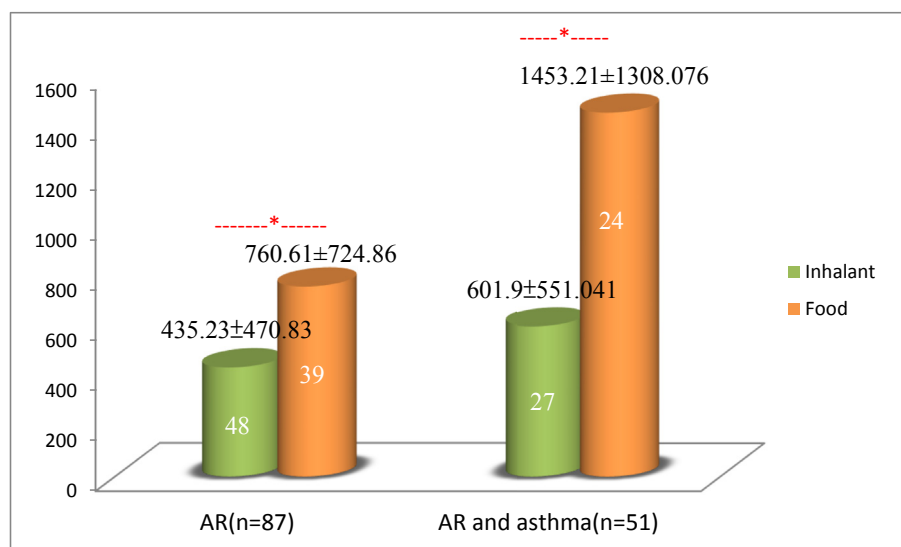
Based on the detection of allergen-specific IgE by ImmunoCAP testing, the four types of house dust mite (HDM), including Der p, Der f, Der m and Blot f, were the most common allergens in all the study subgroups, especially to HDM, Der p, Der m and Blot f were above 80%, respectively. Crab (23% and 27.5%) and shrimp (20.7% and 25.5%) were the most common food allergens in each AR food group and Asthma food group (Table 2).

Discussion

This study demonstrated that children with cosensitized to food and inhalant allergens have more severe clinical symptoms and abnormal laboratory findings. There was a higher total IgE levels and PRQLQ scores. Moreover, the allergic rhinitis children with cosensitized to food and inhalant allergens had significantly lower nPEFR values, those had higher PRQLQ scores. The asthma children with

Table 1 Demography of characteristics and baseline data of the two groups and each subgroup.

	Allergic rhinitis (n = 87)			Allergic rhinitis and asthma (n = 51)		
	Non-food	Food		Non-food	Food	
Number	48	39		27	24	
Sex						
Male	27 (56.3%)	22 (56.4%)		15 (55.6%)	16 (66.7%)	
Female	21 (43.7%)	17 (43.6%)		12 (44.4%)	8 (33.3%)	
Age	9.12 ± 3.23	7.01 ± 2.53		8.84 ± 2.61	7.33 ± 2.53	
Height(cm)	134.8 ± 19.32	120.87 ± 15.3		132.58 ± 15.14	121.37 ± 15.92	
Weight(kg)	33.94 ± 15.81	25.21 ± 8.85	p = 0.002	32.778 ± 11.98	23.717 ± 8.29	p = 0.019
Personal Hx						
Allergic rhinitis	48 (100%)	39 (100%)		27 (100%)	24 (100%)	
Asthma	0 (0%)	0 (0%)		27 (100%)	24 (100%)	
Atopic dermatitis	1 (2%)	3 (7.69%)		0 (0%)	3 (1.25%)	
Allergic conjunctivitis	1 (2%)	1 (2.56%)		2 (7.4%)	0 (0%)	
Family Hx						
Father						
Allergic rhinitis	20 (41.67%)	24 (61.54%)		11 (40.74%)	10 (41.67%)	
Atopic dermatitis	1 (2%)	0 (0%)		1 (3.7%)	0 (0%)	
Asthma	0 (0%)	2 (5.13%)		1 (3.7%)	0 (0%)	
Mother						
Allergic rhinitis	21 (43.75%)	16 (41.03%)		20 (74.07%)	16 (66.7%)	
Atopic dermatitis	1 (2%)	2 (5.13%)		0 (0%)	0 (0%)	
Asthma	1 (2%)	2 (5.13%)		1 (3.7%)	0 (0%)	
Siblings						
Allergic rhinitis	16 (33.33%)	17 (40%)		12 (44.44%)	5 (20.83%)	
Atopic dermatitis	0 (0%)	2 (5.13%)		1 (3.7%)	2 (8.33%)	
Asthma	1 (2%)	1 (2.56%)		3 (11.11%)	0 (0%)	

**Figure 1.** Compare two groups of serum total IgE levels. *P < 0.05. Mann–Whitney U test.

cosensitized to food and inhalant allergens had lower lung function test values and asthma control test (ACT) scores than the sensitized to only inhalant allergens group. Most clinical trials have shown that sensitization to inhalant allergen is related pediatric allergic rhinitis and asthma,¹² but there are few clinical trials regarding the sensitization to food allergen.

This study showed that both cosensitized to food and inhalant allergens subgroups were higher total IgE levels than both only sensitized to inhalant allergens subgroups. Clinically, total serum IgE levels have been shown to be associated with the severity of allergies among children.¹⁹ A recent study found that the total serum IgE values were strongly associated with the cosensitization between food

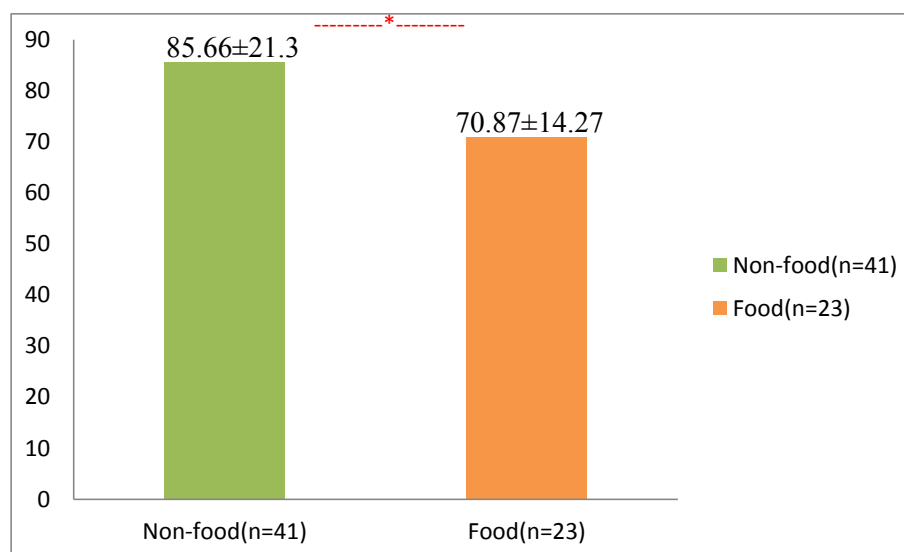


Figure 2. Compare two AR subgroups of nPEFR values. * $P < 0.05$. Mann–Whitney U test.

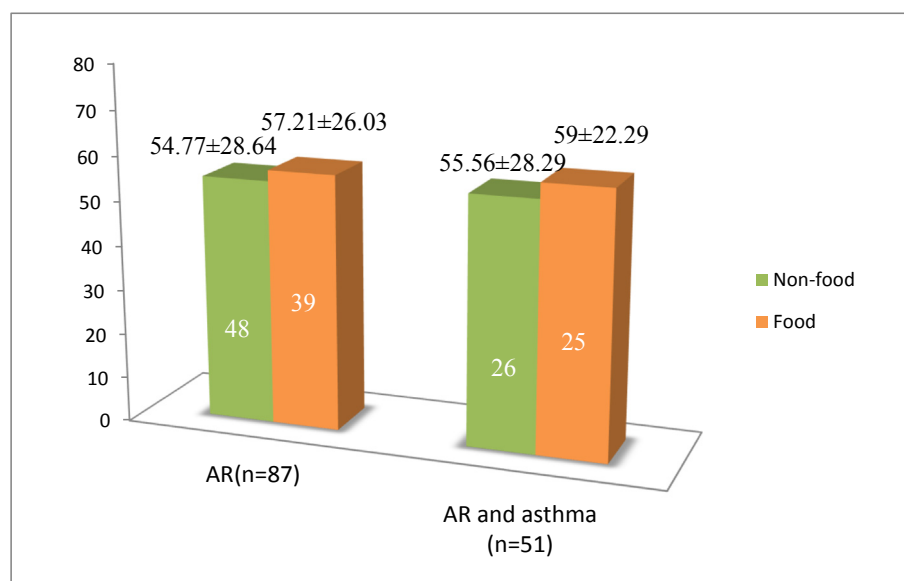


Figure 3. Compare two AR subgroups of mean PRQLQ scores. Mann–Whitney U test.

and inhalant allergens, suggesting that increased IgE values induced by multiple allergen sensitization may contribute to a severe allergic response.²⁰ In the same study, cosensitized to food and inhalant allergens showed a significant risk in relation to atopic diseases, including allergic rhinitis, asthma and eczema, before the age of 2 but it appeared to be more specific to rhinitis and asthma after the age of 2.²³ Similarly, we found that cosensitized to food and inhalant allergens related to allergic rhinitis, but not to asthma with mean age of 8 years.

Foods are common allergens in early childhood. As the child grows, foods are replaced by inhalant allergens.²¹ Kulig M et al. reported describing the natural course of sensitization to food and inhalant allergens showed a decrease in the sensitization to food allergens from 10% at 1

year to 3% at 6 years of age.²² At the same time, sensitization to inhalant allergens increased from 1.5% at 1 year to 26% at 6 years of age. Baatenburg de Jong A et al. revealed that sensitization to food allergens in teenagers is most commonly seen in the context of polysensitization to a mixture of several food and inhalant allergens.²³ Similarly, our study revealed that 63 (39 AR and 24 Asthma) of 138 children were polysensitized to both food and inhalant allergens by the age of 4–18 years. Moreover, Their families has atopic history. Therefore, they are a high-risk atopic group and show more severe clinical symptoms. Our study confirms previous reports that persistently food sensitized children particularly in atopic families have to be regarded as a high-risk group and should be considered for developing severe atopic disease.²⁴

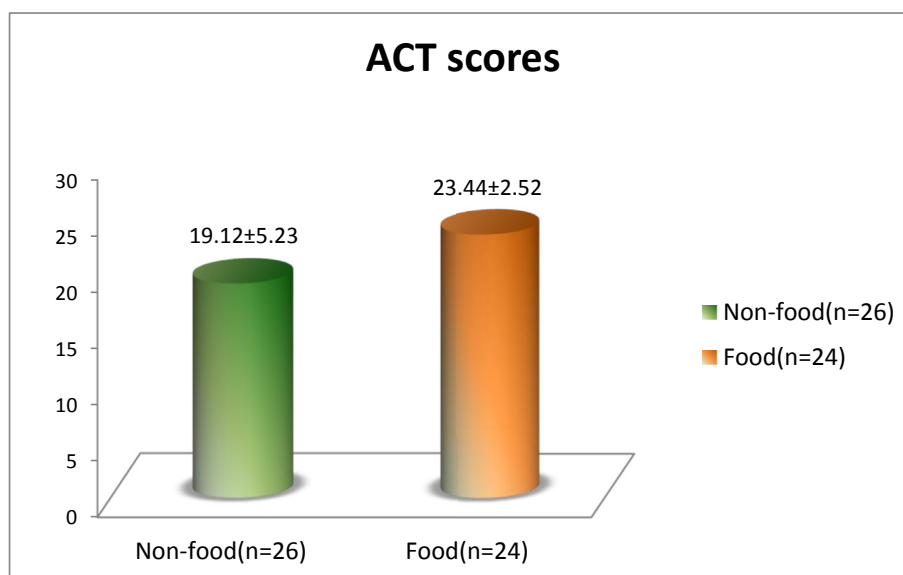


Figure 4. Compare two asthma subgroups of mean ACT scores. *Mann–Whitney U test*.

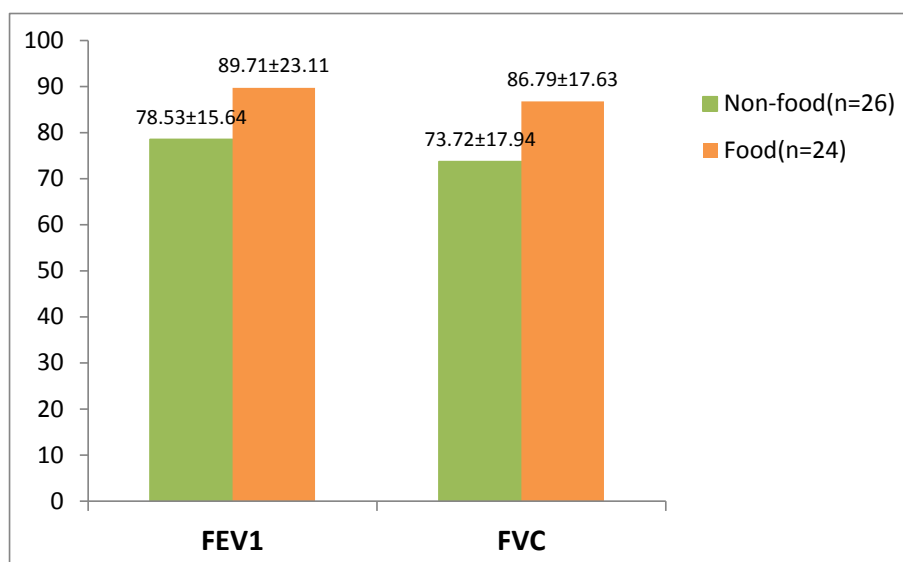


Figure 5. Compare two asthma subgroups of mean FEV1 and FVC values. *Mann–Whitney U test*.

We found that the children in our study had higher rates of sensitization to HDMs (Der p, Der f, Der m, and Blo t), which was predominated in prevalence over food allergens (milk, egg, shrimp, crab and fish). In previous studies from our country revealed Der p and Der f were most common allergens and the most common food allergens were crab and shrimp.^{25–29} These findings are comparable to our results (Table 2). The high sensitization to HDMs is a reflection of the persistence of mite exposure in the environment, which is the principal etiologic agents of respiratory allergies. By comparison, food allergens are relatively rare triggers of acute asthma attacks. Inhaled allergens (e.g., HDMs, grass pollens, and animal dander) rather than food allergens contribute to airway inflammation in asthma.²⁵ In this study, we found that asthma food group (asthma children with cosensitized to food and inhalant allergens) had

poor lung function and asthma control than the other group.

This study found that children with cosensitized to food and inhalant allergens had a lower BMI than inhalant allergens alone. Several studies revealed that there were associated between allergic respiratory diseases and obesity. However, increased BMI and allergic respiratory diseases, such as asthma and allergic rhinitis, may be related.^{30–37} Indeed, Colombo BM et al. suggested that BMI seems to be associated with the development of Th2 diseases such as allergic rhinitis and asthma, but not with Th1 diseases such as SLE.³⁸ Because both allergic respiratory diseases and obesity are characterized by inflammation, a common inflammatory pathway has been proposed as a plausible explanation for the association between respiratory allergy and obesity. In the contrary, a Chinese study

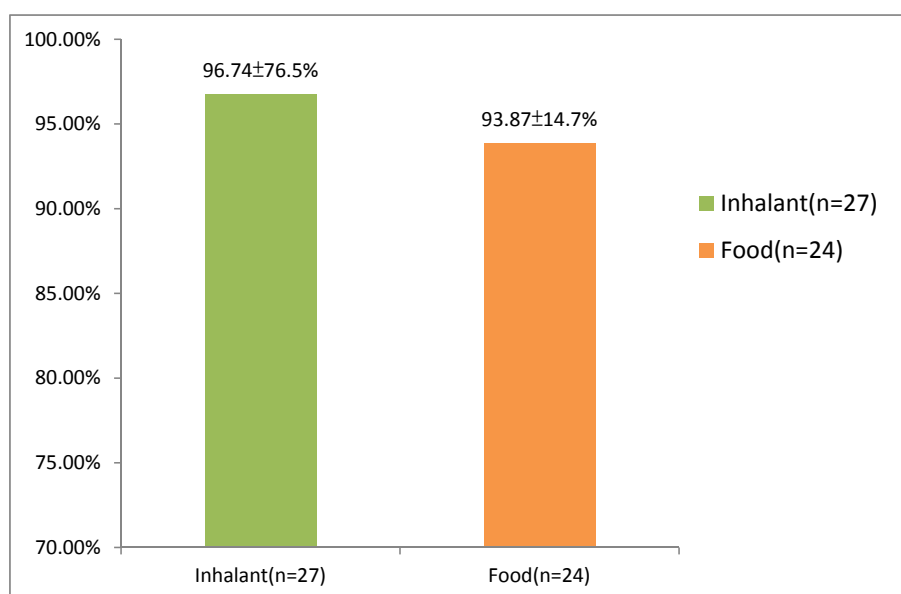


Figure 6. Compare two asthma subgroups of mean FEV1/FVC ratio values. *Mann–Whitney U test.*

Table-2 Different allergen sensitization profiles of two groups.

Allergen	Allergic rhinitis (n = 87)	Asthma (n = 51)
House dust mite (n = 125)	77 (88.5%)	48 (94.1%)
Der p (n = 135)	85 (97.7%)	50 (98%)
Der f (n = 125)	76 (87.4%)	49 (96.1%)
Der m (n = 122)	74 (85.1%)	48 (94.1%)
Blomia tropicalis (n = 112)	66 (75.9%)	46 (52.9%)
Dog epithelia (n = 9)	7 (8%)	2 (3.9%)
Cat epithelia (n = 4)	2 (2.3%)	2 (3.9%)
Cockroaches (n = 39)	17 (19.5%)	22 (43.1%)
Aspergillus fumigatus (n = 0)	0 (0%)	0 (0%)
Candida albicans (n = 1)	1 (1.1%)	0 (0%)
Cladosporium (n = 3)	1 (1.1%)	2 (3.9%)
Penicillium (n = 1)	1 (1.1%)	0 (0%)
Bermuda grass (n = 23)	15 (17.2%)	8 (15.7%)
Timothy grass (n = 14)	9 (10.3%)	5 (9.8%)
Ragweed (n = 1)	1 (1.1%)	0 (0%)
Milk (n = 26)	16 (18.4%)	10 (19.6%)
Egg white (n = 24)	15 (17.2%)	9 (17.6%)
Crab (n = 34)	20 (23%)	14 (27.5%)
Shrimp (n = 31)	18 (20.7%)	13 (25.5%)
Codfish (n = 10)	4 (4.6%)	6 (11.8%)

showed that obesity was not associated with asthma, allergic rhinitis and eczema. In addition, there was absence of any consistent relationship between obesity status and atopy.³³ Similarly, we did not find any association between body weight and allergic respiratory diseases. However, children with food sensitization had a lower body weight, which, we consider it to be a result of a restricted diet imposed by parents for preventing allergic symptoms.

Our study is limited by the relatively small sample size, differential severity of diseases and lack of data on environmental exposures (e.g., tobacco smoke, ethnicity, physical exercise and parasitic infestation), which may modulate serum total IgE.^{34–36} We used the specific-serum IgE test, but not the skin prick test (SPT). The sensitivity of serum-specific IgE testing is generally considered less sensitive than SPT. Nonetheless, serum-specific IgE testing is recommended as a first-line diagnostic procedure in patients highly suspected with atopic diseases on the basis of clinical status and history.^{8,9,37,39–41} In addition, The Pharmacia second-generation ImmunoCAP method is widely used and has generated adequate results compatible to the skin prick test.^{5–7} The methodologic strengths of this study include low missing data rates, low drop-out rate, additional testing obtained, such as PRQLQ, nPEFR, ACT/C-ACT and lung function test; as well as the younger mean age. Furthermore, this study is a prospective assessment for evaluating the impact of food allergen sensitization and clinical outcomes in our atopic children.

In conclusion, our study showed that children with cosensitized to food and inhalant allergens have more severe clinical symptoms and abnormal laboratory findings. Sensitization to food allergens was more related to pediatric allergic rhinitis than asthma. We may need larger, longer and extended studies to confirm these findings.

Financial support

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Conflicts of interest

All authors have no such interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jmii.2019.01.005>.

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