

ORIGINAL ARTICLE

Correlation of ovalbumin of egg white components with allergic diseases in children



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KEYWORDS

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Background: Immunoglobulin E (IgE)-mediated food allergy, such as egg white allergy, is common in young children (<3 years old), but not all young children sensitive to egg white present with allergic symptoms. This study investigated the relationship between sensitization to egg white component allergens and clinical manifestations of allergic diseases in young children. **Methods:** From March to December 2010, 2256 children with physician-diagnosed allergic diseases were tested for serum levels of egg white, ovalbumin, and ovomucoid-specific IgE in the Pediatric Allergy and Asthma Center of Chang Gung Memorial Hospital. Serum was analyzed for specific IgE antibodies to egg white, ovalbumin, and ovomucoid by ImmunoCAP (Phadia, Uppsala, Sweden). Allergen-specific IgE levels ≥ 0.35 kU_A/L were defined as positive.

Results: There was a significantly higher sensitization rate to egg white and its components in children aged 2–4 years old. The sensitization rate to egg white, ovalbumin, and ovomucoid in this age group was 53.5%, 48.3%, and 37.2%, respectively, and the trend of the sensitization decreased with age ($p < 0.001$). After adjusting for age, sensitization to egg white and ovalbumin was associated with children with dermatitis [egg white: odds ratio (OR) = 1.28, 95% confidence intervals (CI) = 1.03–1.58, $p < 0.05$; ovalbumin: OR = 1.30, 95% CI = 1.04–1.62, $p < 0.05$]. Children with ovomucoid sensitization had no statistically significant risk among different groups in the current study.

Conclusion: Children aged 2–4 years old have higher sensitivity to egg white, ovalbumin, and ovomucoid. Children with egg white and ovalbumin sensitization have a higher risk for atopic dermatitis, and ovalbumin has a more important contribution. Furthermore,

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we suggested that in children with atopic dermatitis, if they are aged 2–4 years old and are having egg white and ovalbumin sensitization, avoiding eating raw or slightly heated eggs might have a beneficial effect.

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Introduction

Food allergy results from the immune system mistakenly identifying certain foods as harmful, thereby producing food-specific immunoglobulin E (IgE) that leads to various immune reactions. The prevalence of food allergy is highest in infancy, with milk and egg as the most commonly identified allergens.¹ The body encounters eggs mostly through the mouth or skin, such that allergic reactions can happen in the gastrointestinal tract and skin, and manifest as erythema, urticaria, and eczematous rash, and as abdominal pain and vomiting.² Egg allergy is closely associated with allergic diseases, particularly in infants who have eczema within 1 year of age.^{3–5} Even though anaphylactic reactions due to egg allergy are uncommon clinically, literature shows that severe food allergy is associated with asthma later in life.⁶ Similarly, compared to children without food allergy, those with food allergy have an increased incidence of other atopic diseases like asthma, eczema, or respiratory allergy.⁷

According to the atopic march theory, a diagnosis of eczema and food allergen sensitization in infancy increases the probability of having asthma and allergic rhinitis at school age.⁸ Moreover, egg sensitization in infancy increases the possibility of sensitization to aeroallergens⁹ and later developing asthma.¹⁰

Food allergy is diagnosed based on clinical reactivity to food contact and IgE tests (i.e., skin prick tests and/or antigen-specific IgE in serum). In recent years, multiple component allergenic proteins have been found in egg white. Ovomuroid (Gal d1, 11%), ovalbumin (Gal d2, 54%), ovotransferrin or conalbumin (Gal d3, 12%), and lysozyme (Gal d4, 3.4%) have been identified as the major allergens.¹¹ The heat and acid-stable characteristics of ovomuroid enable it to possess strong allergenicity, making it the dominant allergen.¹² Järvinen et al¹³ found that children with persistent egg allergy had higher serum concentrations of ovomuroid-specific IgE when compared to those with transient egg allergy. Moreover, it has been reported that allergy to heat-treated egg can be diagnosed effectively by measuring the serum concentration of ovomuroid-specific IgE. Ando et al¹⁴ showed that when serum concentration of IgE antibody specific to egg white was >7.38 kU_A/L, the individual had an increased risk of having raw egg allergy. Similarly, when specific IgE antibody levels to ovomuroid are >10.8 kU_A/L, the individual has an increased risk of having an allergic reaction to heat-treated and raw eggs.

Although ovalbumin is the most abundant protein in egg white, it is heat-labile and undergoes conformational changes to become more stable, thereby making it less allergenic.¹⁵ Similarly, ovotransferrin and lysozyme also appear to be less important in the pathogenesis of egg allergy. Some studies show that patients who are allergic to egg and who are having specific-IgE antibodies to lysozyme

may have allergic reactions when exposed to egg lysozyme in hidden forms in pharmaceutical products and foods.¹⁶ Ovalbumin, ovotransferrin, and lysozyme all are heat-labile proteins, therefore, the risk for a clinical reaction to cooked egg is relatively low.¹⁷

However, studies on the association of egg white component proteins and allergic diseases are unavailable to date. The present study investigates the relationship between sensitization to egg white component allergens and the clinical manifestations of allergic diseases, including asthma, atopic dermatitis, and allergic rhinitis.

Patients and methods

Study population

From March to December 2010, 2256 children with physician-diagnosed allergic diseases (i.e., asthma, allergic rhinitis, or atopic dermatitis) in the Pediatric Allergy and Asthma Center of Chang-Gung Memorial Hospital were enrolled. Patients (age range = 0.1–17.6 years; mean age = 5.09 years; boy-to-girl ratio = 1350:906) were categorized into seven groups according to diagnosis: Group A, patients with asthma only ($n = 133$); Group B, patients with allergic rhinitis only ($n = 496$); Group C, patients with atopic dermatitis only ($n = 58$); Group D, patients with both asthma and allergic rhinitis ($n = 1077$); Group E, patients with both asthma and atopic dermatitis ($n = 37$); Group F, patients with both atopic dermatitis and allergic rhinitis ($n = 270$); Group G, patients with asthma, atopic dermatitis, and allergic rhinitis simultaneously ($n = 185$).

In total, 1432 patients were diagnosed with asthma (Groups A, D, E, and G), 2028 had allergic rhinitis (Groups B, D, F, and G), and 550 had atopic dermatitis (Groups C, E, F, and G) (Fig. 1).

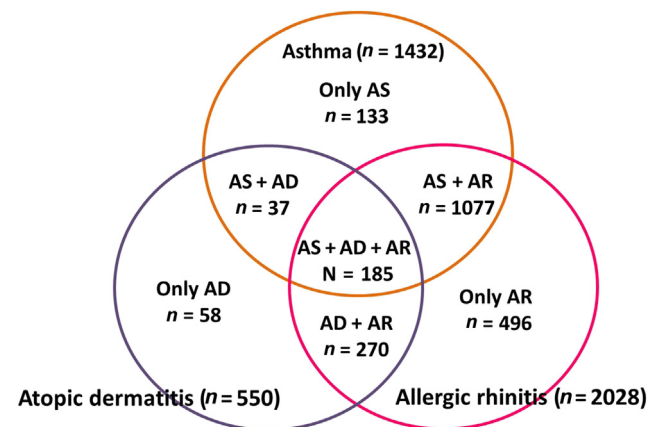


Figure 1. The diagnostic subgroup of patients ($n = 2256$). AD = atopic dermatitis; AR = allergic rhinitis; AS = asthma.

Determination of sensitization

All patients were tested for serum levels of IgE antibodies specific to egg white, ovalbumin, and ovomucoid by ImmunoCAP (Phadia, Uppsala, Sweden). Allergen-specific IgE levels between 0.35 and 100 kU_A/L were recorded and a serum level ≥ 0.35 kU_A/L was defined as sensitization.

Statistical analysis

The positive sensitization rate to egg white components among different age groups was compared by the Mann-Whitney test, while serum IgE levels of egg white components among different age groups were compared by ANOVA *post hoc* Tukey test. Logistic regression was used to evaluate the relationship between sex, age, and egg white components in relation to the likelihood of allergic diseases. Odds ratios (OR) were estimated using the regression models and confidence intervals (CI) were generated according to Wald, using $p < 0.05$ as significant.

Results

Distribution of sex, age, and egg white components according to diagnosis

There were more boys than girls in all groups and the peak age was in the range of 2–4 years in all groups, except the 0–2 year-olds for Group C and the 4–6 year-olds for Group D (Table 1). Egg white was the most common sensitizing protein, followed by ovalbumin, with ovomucoid as the least common. Group E children had higher positive sensitization rates to egg white (51.4%), ovalbumin (48.6%), and ovomucoid (32.4%) than the other groups, while children in group B had lower positive sensitization rates at 30.2%, 27.6%, and 21.2%, respectively (Table 1). Furthermore, 788 children (34.9%) were sensitized to egg white, including 129 patients who were not sensitized to ovalbumin, 310 not sensitized to ovomucoid, and 70 not sensitized to both ovalbumin and ovomucoid (data not shown).

Association between different age groups and allergic diseases

Analyzing the association of allergic diseases among different age ranges with age 0–2 arbitrarily set as the reference, individuals were more likely to have allergic diseases at younger age ranges in Groups A, C, E, and F, and in children with atopic dermatitis. Children with allergic rhinitis were more likely to have the disease at older age ranges. In Group B, children aged 9–18 years old were more likely to have the disease, while in Group G, children aged 2–4 years old had the highest risk.

In children with asthma, there was a higher risk in those aged 0–12 years, with the highest risk in those aged 4–6 years. In Group D, children aged 0–18 years were more likely to have allergic disease and those aged 4–6 years had the highest risk (Table 2).

IgE levels and positive sensitization rates in different age groups

Analyzing serum levels of IgE antibodies specific to egg white, ovalbumin, and ovomucoid among different age ranges showed that IgE levels were highest among children aged 0–2 years, with decreasing titers as age increased (Fig. 2A, children aged 0–2 years were arbitrarily set as the reference). Positive sensitization to egg white components was most prevalent in children aged 2–4 years. The positive rates were 53.5% for egg white, 48.3% for ovalbumin, and 37.2% for ovomucoid. As the children got older, sensitization to egg white and its two components decreased gradually (Fig. 2B, children aged 2–4 years were arbitrarily set as the reference). The different age ranges also had a statistically significant impact on serum concentrations of specific IgE against egg white component as, well as the positive rates of sensitization (Fig. 2A and 2B).

Association between sensitization to egg white components and allergic diseases

Egg white and ovalbumin sensitization were associated with Group E and atopic dermatitis (egg white, OR = 1.99, 95% CI = 1.04–3.81, $p < 0.05$; ovalbumin, OR = 2.25, 95% CI = 1.18–4.32, $p < 0.05$) and (egg white, OR = 1.37, 95% CI = 1.13–1.67, $p < 0.01$; ovalbumin, OR = 1.45, 95% CI = 1.18–1.77, $p < 0.001$), respectively. Furthermore, sensitization to ovalbumin was associated with Group F (OR = 1.34, 95% CI = 1.03–1.75, $p < 0.05$). By univariate analysis, the OR of egg white sensitization for Group B children were significantly lower than those of other groups ($p < 0.05$) and the OR of ovalbumin sensitization for Group D children were also significantly lower than those of other groups ($p < 0.05$) (Table 2).

After adjusting for confounding factors such as sex, age, and sensitization to egg white component allergens in multivariate analysis, egg white and ovalbumin sensitization remained associated with children with atopic dermatitis (egg white, OR = 1.28, 95% CI = 1.03–1.58, $p < 0.05$; ovalbumin, OR = 1.30, 95% CI = 1.04–1.62, $p < 0.05$). However, there was no statistically significant association between other allergic diseases and risk factors (Table 3).

Discussion

The present study has several significant findings. First, the positive sensitization rate of each egg white component allergen peaks at the age of 2–4 years in Taiwanese children with allergic diseases. Second, egg white and ovalbumin sensitization are significantly associated with children with atopic dermatitis. Third, children with ovomucoid sensitization had no statistically significant risk among different allergic disease groups.

In this study, there are more boys than girls diagnosed with allergic diseases (i.e., asthma, allergic rhinitis, or atopic dermatitis). However, there is no statistically significant difference between gender in terms of allergic

Table 1 Distribution of different allergic diseases by sex, age, and sensitization to egg white allergens

Groups	A	B	C	D	E	F	G	All	Any AS	Any AR	Any AD
Total	133	496	58	1077	37	270	185	2256	1432	2028	550
Male	78	303	35	656	20	152	106	1350	860	1217	313
(%)	(58.6)	(61.1)	(60.3)	(60.9)	(54.1)	(56.3)	(57.3)	(59.8)	(60.1)	(60)	(56.9)
Female	55	193	23	421	17	118	79	906	572	811	237
(%)	(41.4)	(38.9)	(39.7)	(39.1)	(45.9)	(43.7)	(42.7)	(40.2)	(39.9)	(40)	(43.1)
Age (y)											
0–2	33	51	30	42	14	73	16	259	105	182	133
(%)	(24.8)	(10.3)	(51.7)	(3.9)	(37.8)	(27.0)	(8.6)	(11.5)	(7.3)	(9.0)	(24.2)
2–4	44	154	16	340	19	89	73	734	475	655	197
(%)	(33.1)	(31.0)	(27.6)	(31.6)	(51.4)	(33.0)	(39.5)	(32.5)	(33.2)	(32.3)	(35.8)
4–6	35	111	3	382	3	44	47	624	466	583	97
(%)	(26.3)	(22.4)	(5.2)	(35.5)	(8.1)	(16.3)	(25.4)	(27.6)	(32.5)	(28.7)	(17.6)
6–9	15	71	3	201	1	33	20	345	238	326	57
(%)	(11.3)	(14.3)	(5.2)	(18.7)	(2.7)	(12.2)	(10.8)	(15.3)	(16.6)	(16.1)	(10.4)
9–12	5	69	5	84	0	16	20	200	110	190	41
(%)	(3.8)	(13.9)	(8.6)	(7.8)		(5.9)	(10.8)	(8.9)	(7.7)	(9.4)	(7.5)
12–18	1	40	1	28	0	15	9	94	38	92	25
(%)	(0.8)	(8.1)	(1.7)	(2.6)		(5.6)	(4.9)	(4.2)	(2.7)	(4.5)	(4.5)
Allergen sensitization											
Egg white	47	150	20	368	19	108	76	788	510	702	223
(%)	(35.3)	(30.2)	(34.5)	(34.2)	(51.4)	(40.0)	(41.1)	(34.9)	(35.6)	(34.6)	(40.5)
Ovalbumin	43	137	17	298	18	96	67	676	426	598	198
(%)	(32.3)	(27.6)	(29.3)	(27.7)	(48.6)	(35.6)	(36.2)	(30)	(29.7)	(29.5)	(36.0)
Ovomucoid	35	105	12	267	12	63	55	549	369	490	142
(%)	(26.3)	(21.2)	(20.7)	(24.8)	(32.4)	(23.3)	(29.7)	(24.3)	(25.8)	(24.2)	(25.8)

Group A = patients with asthma (AS) only; Group B = patients with allergic rhinitis (AR) only; Group C = patients with atopic dermatitis (AD) only; Group D = patients with both asthma and allergic rhinitis; Group E = patients with both asthma and atopic dermatitis; Group F = patients with both atopic dermatitis and allergic rhinitis; Group G = patients with asthma, atopic dermatitis, and allergic rhinitis simultaneously.

diseases. Also most cases of allergic diseases were found in children aged 2–4 years. Moreover, children with atopic dermatitis are most likely to be among the younger age group and those with allergic rhinitis are most likely to be among the older age group, while those with asthma are in

the mid-age range. These results are similar to those of previous studies.^{8,18}

Although it is a common allergen in infancy and children, egg white sensitization decreased with age.^{19,20} Wan et al²¹ demonstrated that the prevalence of egg white

Table 2 Logistic regression analysis of the association of allergic diseases with sex, age, and sensitization to allergens

Groups	A	B	C	D	E	F	G	Any AS	Any AR	Any AD
Sex										
Female	1.05	0.93	0.98	0.92	1.27	1.18	1.12	0.97	0.93	1.17
Age (y)										
0–2	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2–4	0.47*	1.77	0.18*	4.72*	0.50	0.38*	1.79*	2.91*	3.75*	0.40*
4–6	0.44*	0.96	0.04*	8.70*	0.05*	0.21*	1.33	4.74*	6.55*	0.20*
6–9	0.34*	1.15	0.07*	7.71*	0.09*	0.30*	1.01	3.54*	7.14*	0.22*
9–12	0.19*	2.35*	0.21*	4.07*	–	0.25*	1.83	1.98*	7.99*	0.29*
12–18	0.08*	3.07*	0.09*	2.25*	–	0.51*	1.66	1.05	7.22*	0.38*
Allergen sensitization										
Egg white	1.02	0.76*	0.98	0.94	1.99*	1.28	1.33	1.08	0.89	1.37*
Ovalbumin	1.13	0.87	0.97	0.82*	2.25*	1.34*	1.37	0.98	0.86	1.45*
Ovomucoid	1.11	0.79	0.80	1.03	1.49	0.93	1.34	1.21	0.88	1.10

* $p < 0.05$, by logistic regression.

Note: Group E had no individuals aged 9–18 years of age.

AD = atopic dermatitis; AR = allergic rhinitis; AS = asthma.

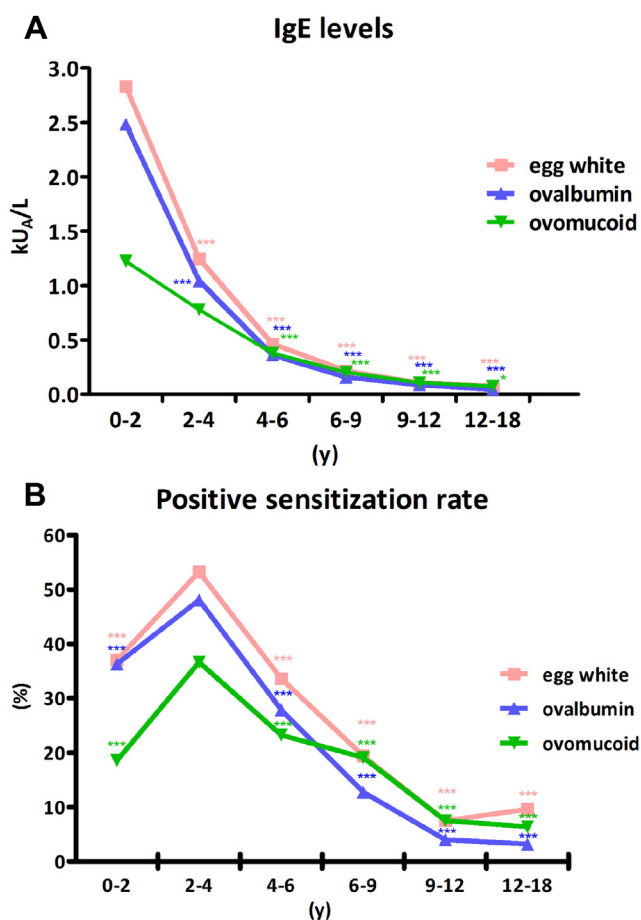


Figure 2. Serum specific IgE levels and positive sensitization rates to egg white, ovalbumin, and ovomucoid in different age groups ($n = 2256$). (A) Serum s-IgE levels for trend (0–2 year age groups are reference); $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, by ANOVA *post hoc* Tukey test; (B) positive sensitization rates for trend (2–4 age groups are reference); $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, by Mann-Whitney test.

sensitization was 24.23% in children aged 7–8 years in Taipei city. In the present study, the positive sensitization rate of egg white component allergens was 34.9% for egg white, 30.0% for ovalbumin, and 24.3% for ovomucoid in Taiwanese children with allergic diseases, and the highest positive rate for egg white components was found in children aged 2–4 years. In addition, egg white components-specific IgE levels are reduced with increasing age. The

results here show that in children with allergic diseases, serum egg white allergen-specific IgE levels and positive rate are dependent on age. Among these, specific IgE to ovalbumin is more prevalent than that of ovomucoid, probably due to its composition percentage in allergenic egg white proteins.

Previous studies show that egg allergy or egg sensitization is associated with atopic dermatitis,^{3–5} and results of the present study also show similar findings. If the children are further subcategorized according to different allergic diseases, children with simultaneous atopic dermatitis and asthma are more at risk than children with atopic dermatitis only, with atopic dermatitis and allergic rhinitis, and with asthma, atopic dermatitis, and allergic rhinitis simultaneously. This result is in accordance with a previous study by Gaffin et al,²² in which children with egg allergy have significantly greater odds of having asthma. However, after eliminating some possible confounding factors (e.g., age, sex, and egg white components sensitization), there was no statistically significant difference between egg white sensitization and atopic dermatitis with asthma. Thus, age, sex, or other confounding factors are mutual confounding factors for children with both atopic dermatitis and asthma.

Although ovalbumin is the most abundant protein in egg white, it is heat-labile and undergoes conformational changes to form more stable but possibly less allergenic structures. The present study shows that children with ovalbumin sensitization are associated with children with atopic dermatitis (including the atopic dermatitis with asthma and the atopic dermatitis with allergic rhinitis subgroups). After controlling for confounding factors, atopic dermatitis and ovalbumin sensitization are related. This is similar to the relationship of egg white sensitization and allergic diseases. Data from the present study also show a strong correlation between the specific IgE (sIgE) level to egg white and ovalbumin ($r = 0.92$), a lower correlation between the sIgE level to egg white and ovomucoid ($r = 0.65$), and the lowest correlation between the sIgE level to ovalbumin and ovomucoid ($r = 0.51$, data not shown). This may imply that ovalbumin is responsible for the association between egg white sensitization and allergic diseases.

Unfortunately, few studies discuss the relationship between egg white components and allergic diseases. A recent study by Kukkonen et al²³ defines the role played by ovalbumin in atopic disease. They found that compared to nonatopic, nonallergic children, those diagnosed with any atopic diseases during 0–2 or 0–5

Table 3 Multivariate analysis of egg white component allergens and their association with allergic diseases

Groups		A	B	C	D	E	F	G	Any AS	Any AR	Any AD
Egg white	OR	1.02	0.76*	0.98	0.94	1.99*	1.28	1.33	1.08	0.89	1.37*
	Adjusted OR	0.87	0.86	0.87	0.95	1.34	1.23	1.30	1.03	1.05	1.28*
Ovalbumin	OR	1.13	0.87	0.97	0.82*	2.25*	1.34*	1.37	0.98	0.86	1.45*
	Adjusted OR	0.94	1.01	0.77	0.85	1.41	1.25	1.34	0.94	1.09	1.30*
Ovomucoid	OR	1.11	0.79	0.80	1.03	1.49	0.93	1.34	1.21	0.88	1.10
	Adjusted OR	1.05	0.87	0.88	0.97	1.23	0.95	1.29	1.10	0.88	1.09

* $p < 0.05$, by logistic regression.

AD = atopic dermatitis; AR = allergic rhinitis; AS = asthma; OR = odds ratio.

years of age had higher egg-specific IgE levels and egg-IgE/ovalbumin-IgG₄. Furthermore, with any food allergy, ovalbumin-IgG₄ levels and ovalbumin-IgG₄/egg-IgE are lower than those of nonallergic, nonatopic individuals. IgG₄ antibody is a marker of development of food tolerance and IgG₄ antibodies have been proposed to act as blocking antibodies by competing with IgE for allergen binding to IgE receptor expressing cells.²⁴ By contrast, IL-10 secreted by inducible T regulatory cells increases IgG₄ production but inhibits IgE production.²⁵ It is proposed that the titer of ovalbumin-IgG₄ antibodies decreases but that of ovalbumin-IgE antibodies increases in atopic or allergic diseases. This hypothesis supports the results of the present study, that in children with atopic dermatitis, serum egg-white and ovalbumin-specific IgE levels are high. Tomićić et al²⁶ also report that sensitized, eczematous infants with high ratios of IgG₄/IgE to ovalbumin at an early age are more likely to tolerate egg at 4.5 years than infants with low ratios. They also reveal that the ovalbumin-IgG₄-to-IgE ratio can be used to predict the development of egg tolerance later in life. Caubet et al²⁷ also found that the combination of specific IgE and IgG₄ is better than specific IgE alone in predicting reactivity to baked egg.

The heat and acid-stable characteristics of ovomucoid can be used to predict the persistence of egg and/or baked egg allergies.^{13,14} However, the role of ovomucoid-specific IgE in atopic or allergic diseases is not fully known at present. The results here show that ovomucoid sensitization does not affect the possibility of having allergic diseases, but implies that the association of egg sensitization with atopic dermatitis is mainly due to ovalbumin, not ovomucoid.

In children with allergic diseases in Taiwan, the positive rates of egg white, ovalbumin, and ovomucoid sensitization are highest in those aged 2–4 years. Children with egg white sensitization also have a high risk of having asthma with atopic dermatitis, but not allergic rhinitis alone. Furthermore, children sensitized to ovalbumin are more likely to have asthma with atopic dermatitis, atopic dermatitis with allergic rhinitis, or atopic dermatitis, but are less likely to have asthma with allergic rhinitis. After controlling for confounding factors, children with egg white and ovalbumin sensitization are still more likely to have atopic dermatitis. Children with ovomucoid sensitization had no statistically significant risk among different allergic disease groups. Furthermore, we suggested that in children with atopic dermatitis, if they are aged 2–4 years old and are having egg white and ovalbumin sensitization, avoiding eating raw or slightly heated egg might have a beneficial effect.

Conflicts of interest

All authors declare no conflicts of interest in this study.

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