

Prevalence and Impact of Past History of Food Allergy in Atopic Dermatitis

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ABSTRACT

Background: Increases in allergic diseases have been reported from various epidemiological surveys. However, a few reports demonstrate the comorbidity of food allergy (FA) and allergic march. The aim of this study was to assess the prevalence and comorbidity of allergic diseases in Japanese students.

Methods: First-year students ($n = 3,321$; 2,209 male and 1,112 female) at Osaka University were asked about allergic diseases using postal interview sheets. Personal and family histories of doctor-diagnosed allergic diseases, clinical courses, and aggravating factors were included in the questionnaires.

Results: The lifetime prevalence of allergic rhinitis (AR), atopic dermatitis (AD), bronchial asthma (BA), and FA was 35.7%, 16.5%, 9.9%, and 7.0%, respectively. Disease-specific family histories existed for AR, AD, and BA. There was a positive correlation between the number of family histories of allergic disease and comorbidity ($R = 0.370$, $P < 0.001$). Comorbidity with AD significantly lowered the onset age of both BA ($P = 0.010$) and AR ($P < 0.001$). In addition, the onset age of AD was remarkably lowered by comorbidity with FA ($P < 0.001$). Comorbidity with FA was the highest risk factor for the progression of allergic march. Although most students showed improvement in AD, BA, and AR over time, the peak recurrence period was observed in adolescence.

Conclusions: These findings indicate that AD associated with FA accelerates the subsequent progression of allergic march. Early appropriate management for genetically high-risk groups is important for the prevention of allergic march.

KEY WORDS

allergic march, atopic dermatitis, epidemiology, food allergy, questionnaire

INTRODUCTION

Increases in allergic diseases, including atopic dermatitis (AD), bronchial asthma (BA), and allergic rhinitis (AR), over the last 30-40 years has been well documented worldwide.¹ Allergic diseases are also an important public health problem because they significantly increase socioeconomic burden by lowering the quality of life and work productivity^{2,3} of affected patients and their families.⁴

“Allergic march” refers to a subset of allergic disorders that commonly begin in early childhood, such as food allergies (FAs), AD, BA, and AR. AD and FA have the highest incidence in the first 2 years of life.⁵ In infancy, sensitization to inhalant allergen is rare. In later childhood, the prevalence of AD, FA, and food

allergen sensitization decreases; however, the prevalence of BA, AR, and sensitization to inhalant allergens rises. Approximately one-half of early onset AD and BA cases are outgrown by adulthood.⁶ However, in an increasing number of patients, symptoms persist until adulthood or occur for the first time in adolescence.

Many epidemiological investigations have suggested that FA is a risk factor for the appearance of other allergic disease in later childhood.⁷⁻¹² Early onset AD was found to be associated with high-risk IgE levels in food sensitization.⁸ Although there might be a correlation between allergic march, FA, and AD, there is no report demonstrating allergic march from the viewpoint of comorbidity among AD, BA, and AR in association with FA. The aim of this study is to in-

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investigate how allergic diseases interact with each other and lead to allergic march by a retrospective investigation from birth to the end of adolescence.

METHODS

STUDY POPULATION AND INTERVIEW SHEET

First-year students at Osaka University were administered postal interview sheets in 2011 ($n = 3,414$). The mark sheet interview form consisted of 27 items requesting information about medical histories of atopic diseases (AD, BA, AR, and FA), family histories of atopic diseases (AD, BA, and AR), the clinical courses of each disease (age of onset, improvement, and recurrence), and aggravating factors, except identifying information for the individuals. Approximately 1 month prior to the entrance ceremony, the sheets were sent by mail to the homes of the parents of all students who had passed the entrance exam. We sent the interview sheets to the parents' homes to encourage completion of the questionnaires. The students brought their completed sheets to a health examination after the entrance ceremony. In total, 3,365 interview sheets were returned, including 44 empty answer sheets; therefore, 3,321 sheets were effectively analyzed.

DEFINITION OF ALLERGIC DISEASE IN PERSONAL AND FAMILY HISTORIES

Analyses were applied to the personal and family histories of allergic diseases. Personal histories of AD, BA, AR, and FA were based on a doctor's diagnosis at any time during the student's life from birth to the present. Family histories of AD, BA, and AR of the father, mother, siblings, and others were based on self-reported diagnoses. The most recent event was reported as the age of improvement and/or recurrence.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 19.0 for Windows. The chi-square test was used for comparisons between categorical variables. The age at which each event occurred during the clinical course (onset, improvement, and recurrence) was compared using the unpaired Student's *t* test for all dichotomous variables and by analysis of variance (ANOVA) for more than three variables. For each disease, family histories and the relationships between events and background factors were evaluated by odds ratios (OR) and 95% confidence intervals (CI) with univariate logistic regression analysis. For prediction of these events, multivariate logistic regression models were evaluated using a backward stepwise selection method. In all analyses, a *P* value less than 0.05 was considered significant.

Table 1 General characteristics of the study subjects

Personal history	<i>n</i> (% [†])	Male (% [‡])	Female (% [‡])
Total	3,316 (100%)	2,209 (66.5)	1,112 (33.5)
AD	547 (16.5)	353 (64.5)	194 (35.5)
BA	329 (9.9)	252 (76.6)	77 (23.4)
AR	1,186 (35.7)	834 (70.3)	352 (29.7)
FA	233 (7.0)	155 (66.5)	78 (33.5)
None of the above diseases	1,739 (52.4)	1,115 (64.1)	624 (35.9)

AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis; FA, food allergy.

[†]denominator of the ratio is 3,321.

[‡]denominator of the ratio is the total number (*n*) of each disease.

RESULTS

LIFETIME PREVALENCE OF ALLERGIC DISEASES

The mean age of the first-year students ($n = 3,321$) was 18.40 ± 0.85 years (range: 18-41 years). In these students, the lifetime prevalence of any atopic disease from birth to the present was 47.6% ($n = 1,582$) and was significantly higher in males than females (49.52% vs. 43.88%, $P = 0.002$). A majority (52.4%; $n = 1,739$) of the students had no medical history of allergic disease (Table 1).

The lifetime prevalence of each disease based on medical diagnoses was as follows (from highest to lowest prevalence): AR (35.7%, $n = 1,185$), AD (16.5%, $n = 547$), BA (9.9%, $n = 329$), and FA (7.0%, $n = 233$). Both AR ($P < 0.001$) and BA ($P < 0.001$) were significantly more prevalent in males than in females. There were no significant differences between genders in terms of lifetime prevalence of AD and FA (Table 1). The age at diagnosis for each allergic disease was subdivided by specialty of the medical doctor performing the diagnosis (Fig. 1).

ASSOCIATION OF PERSONAL AND FAMILY HISTORIES

The results of multivariate logistic regression analysis for the association between personal and family histories with the risk of onset for each atopic disease are summarized in Table 2 and Supplementary Table 1-3. AD, AR, and BA showed comorbidity with other diseases. In AD, comorbidity with FA was the highest risk factor (FA > BA > AR) (Table 2, Supplementary Table 1). In BA, AD was the highest risk factor for comorbidity (AD > FA > AR), and in AR, BA was the highest risk factor (BA > AD > AR) (Table 2, Supplementary Table 2, 3). The personal history of each disease raised the risk of prevalence of other atopic diseases (Table 2, Supplementary Table 1-3).

Family history of AD was a significant risk factor

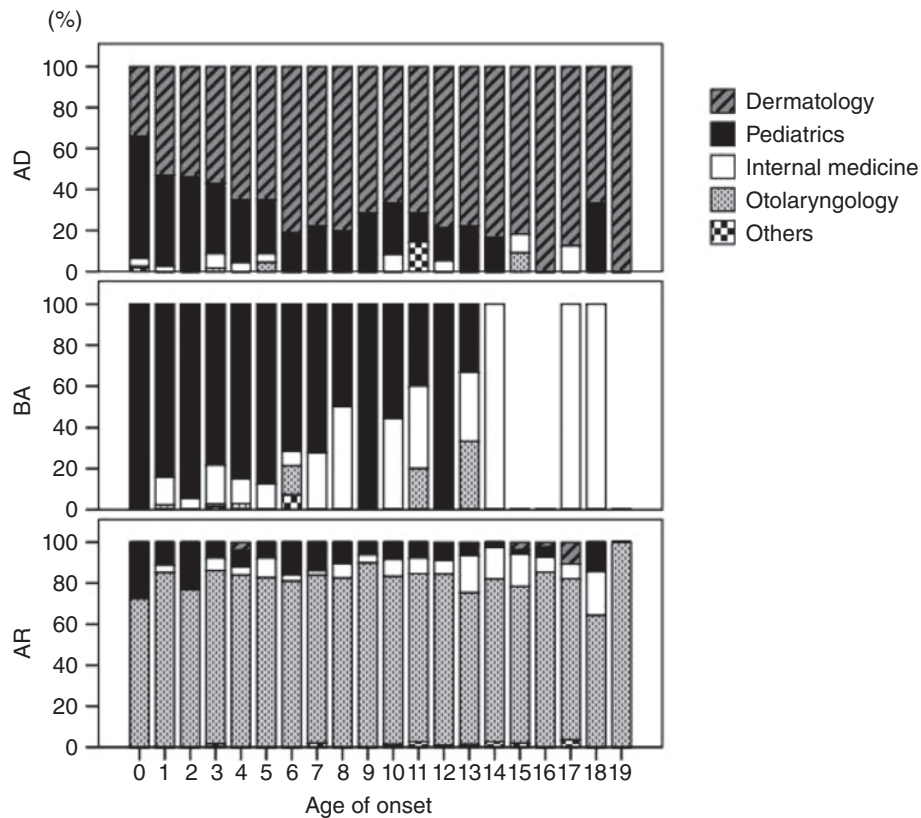


Fig. 1 Age at diagnosis for each allergic disease subdivided by medical specialty of the diagnosing doctor. The ratio of allergic disease diagnosed by specific medical department in each age group. AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis. In students diagnosed with BA, 14 years of age and upward should be used only as a guide because of the few cases examined.

for the development of AD (Table 2, Supplementary Table 1); likewise, family history of BA was strongly associated with the onset of BA and that of AR with the onset of AR (Table 2, Supplementary Table 2, 3). These findings suggest that each atopic disease might have its own specific genetic factor. In addition, there was a positive correlation between the number of allergic conditions (e.g., BA, AD, and AR) in the family history and comorbidity (Pearson's correlation coefficient, $R=0.370$, $P < 0.001$).

EFFECTS OF FA ON ALLERGIC MARCH

From the results presented above, atopic diseases raise the risk of onset for other atopic diseases. We next examined the relationship between the number of atopic diseases, and specifically the comorbidity of such diseases with FA. Atopic diseases were classified in seven categories, and the risk of comorbidity with FA was analyzed for each category: "AD only," "BA only," "AR only," "AD + BA," "AD + AR," "BA + AR," and "AD + BA + AR," using multivariate logistic regression analysis (Table 3). In a category with only a single disease, "AD only" was the most frequent

comorbidity with FA ("AD only" > "BA only" > "AR only"). In a category with two diseases, the risk was as follows: "AD + BA" > "AD + AR" > "BA + AR." The "AD + BA + AR" category was the most frequently observed comorbidity category of all seven categories. Thus, the prevalence rate of each disease increased in association with the number of additional diseases present.

AGE AT ONSET OF ALLERGIC DISEASES

The mean age of onset was compared among three atopic diseases (AD, BA, and AR). There was a significant difference in the mean age of onset: AD onset was at 3.94 ± 4.79 years, BA was at 4.00 ± 3.14 years, and AR was at 9.06 ± 4.71 years (mean \pm SD, ANOVA, $P < 0.001$). The ratios of the age of onset in each of the atopic diseases are summarized in Figure 2. The peak age of onset for AD was earlier than that for BA: a critical peak of AD occurred in early infancy and the peak of BA occurred in childhood. AR developed constantly from early childhood to adolescence.

With regard to improvements in these allergic diseases, there is a peak age during early adolescence

Table 2 Association of personal and family histories with the prevalence of each atopic disease analyzed by multivariate logistic regression analysis

	AD (n = 547)			BA (n = 329)			AR (n = 1,186)		
	% [†]	OR	(95% CI)	% [‡]	OR	(95% CI)	% [§]	OR	(95% CI)
Personal history									
AD				44.4	3.59***	(2.77-4.66)	24.3	1.81***	(1.49-2.21)
BA	26.7	3.59***	(2.76-4.65)				16.4	2.24***	(1.75-2.86)
AR	52.7	1.81***	(1.48-2.21)	59.0	2.25***	(1.77-2.88)			
FA	22.9	5.22***	(3.89-7.01)	23.4	2.96***	(2.13-4.13)	11.3	1.75***	(1.31-2.34)
Family history									
AD									
P	10.4	2.76***	(1.72-4.42)	7.3			4.1	0.61*	(0.37-0.99)
M	13.8	3.85***	(2.50-5.93)	9.5	1.79***	(1.30-2.47)	7.2	1.61*	(1.03-2.52)
S	39.0	3.39***	(2.64-4.32)	30.9			21.3		
O	2.5	2.40	(0.99-5.87)	2.3			1.3		
BA									
P	6.2			12.3	4.22***	(2.54-7.04)	4.4		
M	5.9			10.5	3.62***	(2.10-6.23)	5.2	1.75*	(1.03-2.97)
S	14.9			23.2	2.49***	(1.70-3.67)	10.5		
O	4.5	2.19*	(1.09-4.38)	7.3	5.15***	(2.71-9.81)	2.9		
AR									
P	32.9			33.6	1.29	(0.96-1.73)	39.9	2.46***	(2.01-3.02)
M	40.2	1.28	(1.01-1.63)	43.6	1.37*	(1.04-1.80)	50.1	2.77***	(2.29-3.36)
S	45.8			45.5			52.6	2.43***	(2.02-2.93)
O	2.0			3.2			2.4	5.01**	(1.04-12.54)

AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis; FA, food allergy; P, paternal; M, maternal; S, siblings; O, others.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[†]denominator of the ratio is 547.

[‡]denominator of the ratio is 329.

[§]denominator of the ratio is 1,186.

Table 3 Effect of food allergy (FA) for the onset of allergic march analyzed by multivariate logistic regression analysis

Personal history	n (% [†])	FA		Disease onset risk by complication with FA	
		+ (% [‡])	- (% [‡])	OR	(95%CI)
AD only	217 (6.5)	16.6	83.4	8.70***	(5.47-13.84)
BA only	92 (2.8)	9.8	90.2	4.49***	(2.12-9.54)
AR only	805 (24.2)	5.1	94.9	2.28***	(1.47-3.52)
AD + BA	43 (1.3)	23.3	76.7	12.55***	(5.81-27.14)
AD + AR	185 (5.6)	18.4	81.6	9.33***	(5.76-15.10)
BA + AR	91 (2.7)	14.3	85.7	6.91***	(3.56-13.39)
AD + BA + AR	103 (3.1)	14.9	85.1	32.14***	(19.59-52.74)

AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis; FA, food allergy.

*** $P < 0.001$.

[†]denominator of the ratio is 3,321.

for BA and a peak age for AR during late adolescence (Fig. 2). There are no apparent peaks of improvement for AD, but its prevalence was found in relatively large numbers in both early childhood and during adolescence. With regard to recurrence, all three

atopic diseases presented a peak during adolescence (Fig. 2).

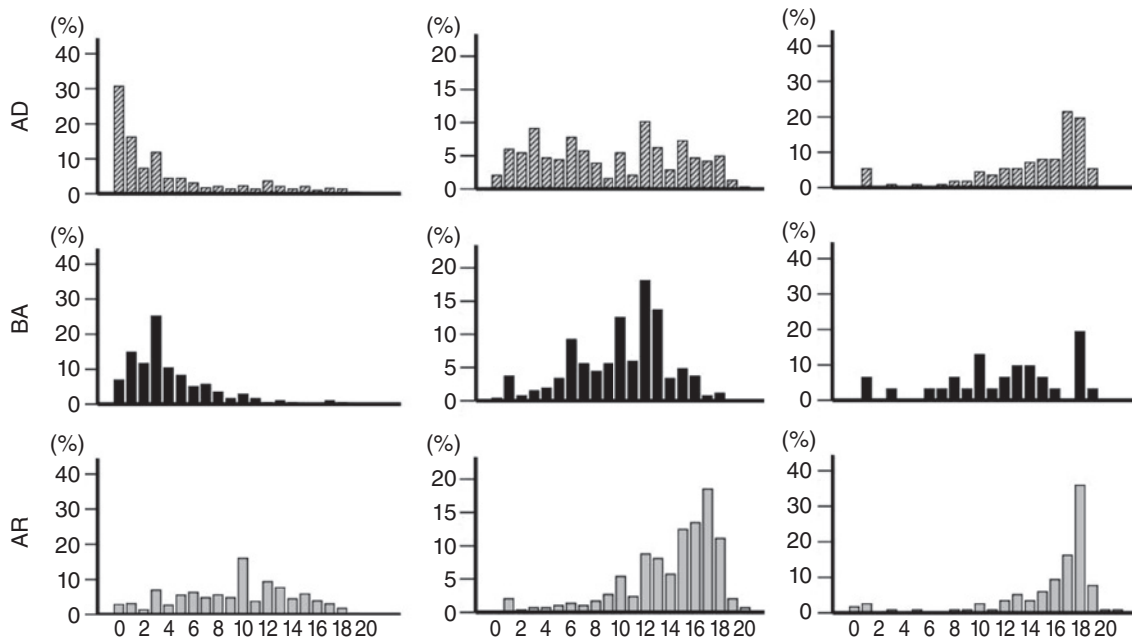


Fig. 2 Clinical course of allergic disease. Clinical course (onset, improvement, and recurrence) of AD (upper), BA (middle), and AR (lower) were demonstrated.

ASSOCIATION FACTORS FOR THE IMPROVEMENT AND RECURRENCE OF AD

Factors associated with the improvement and recurrence of AD symptoms were analyzed (Table 4). The proportion of students who experienced AD improvement was 72.8% in males and 81.5% in females. Early age of onset was associated with more AD improvement than late onset. Among many aggravating factors, xerosis and seasonal changes were most frequently associated with more severe symptoms and less with improvement (Table 4). Subjects with aggravating factors such as psychological stress and sleep disturbances also had significantly high recurrence rates.

EFFECTS OF COMORBIDITY ON ATOPIC DISEASE ONSET

We next analyzed whether the age of onset for each atopic disease was influenced by comorbidity with other atopic diseases. Comorbidity with AD significantly lowered the onset age of BA ($P = 0.010$) and AR ($P < 0.001$) (Fig. 3A). In addition, the onset age of AD was remarkably lowered by comorbidity with FA ($P < 0.001$) and slightly lowered by comorbidity with BA ($P = 0.012$; Fig. 3A). However, the age of onset of BA was not influenced by comorbidity with FA ($P = 0.069$; Fig. 3B) or AR ($P = 0.624$; Fig. 3B). Conversely, the age of onset of AR was significantly lowered by comorbidity with FA ($P < 0.001$), BA ($P < 0.001$), and AD ($P < 0.001$; Fig. 3C).

AD that is comorbid with FA occurs earlier than without FA (Fig. 3A), and BA comorbidity with AD

Table 4 Risk factor link to *improvement* and *recurrence* of atopic dermatitis (AD)

	Covariate	OR (95% CI)	<i>p</i>
Improvement (Yes/No)	Sex (Male/Female)	0.40 (0.24-0.65)	<0.001
	Onset age	0.94 (0.94-0.90)	0.006
	Aggravating factor		
	Xerosis	0.58 (0.37-0.91)	0.019
	Seasonal turning points	0.51 (0.32-0.82)	0.005
Recurrence (Yes/No)	Sweating	0.70 (0.44-1.09)	0.116
	Aggravating factor		
	Psychological stress	4.80 (2.96-7.81)	<0.001
	Sleep	3.03 (1.38-6.67)	0.006

AD, atopic dermatitis.

occurs earlier than without AD (Fig. 3B). Furthermore, AR comorbidity with FA, AD, or BA occurs earlier than without them (Fig. 3C). These data suggest that AD associated with FA accelerates the development of allergic march.

DISCUSSION

Many studies demonstrate the prevalence of allergic diseases; however, most analyzed a limited period from infancy to later childhood and/or to early adolescence. In this study, we retrospectively studied the development of allergic march from birth to late adolescence.

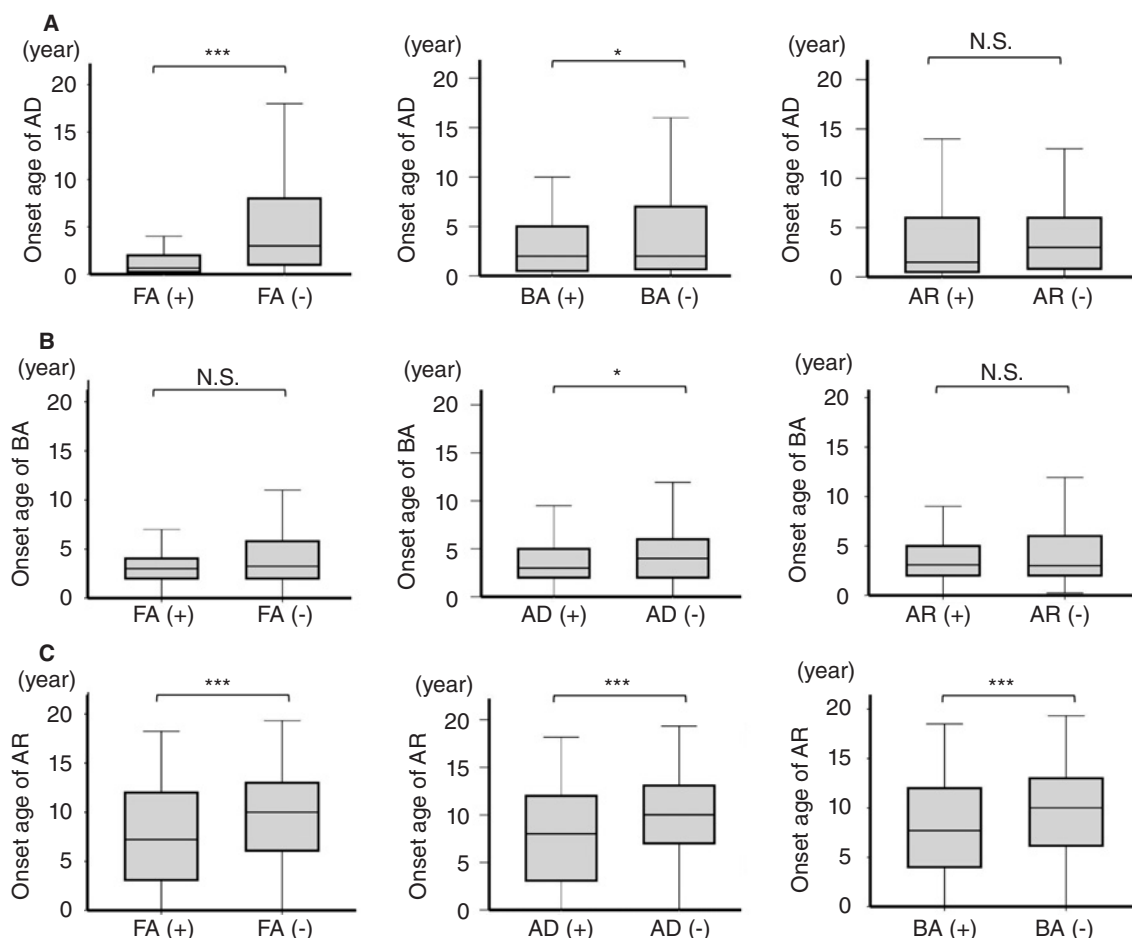


Fig. 3 Effects of comorbidity on the onset of atopic disease. **A:** Onset age was compared in BA and AR by the presence of comorbidity with AD. **B:** The age of onset of AD was compared with comorbid BA, AR, and FA. **C:** Onset age was compared in BA and AR with comorbid FA. * $P < 0.05$, *** $P < 0.001$. N.S., not significant.

In Japan, the lifetime prevalence of AD ranged between 10-16%, 4-7% for BA, and 24-29% for AR among school children.¹³⁻¹⁶ These previous studies showed no consensus with regard to the trend of annual prevalence of AD in school children and adolescents: some previous reports show an increasing prevalence and others show a decreasing prevalence. In the present study, lifetime prevalence of AD and BA was almost identical with previous studies, but that of AR was higher.

There is disease specificity in the relationship between family history and the lifetime prevalence of allergic diseases. Subjects with AD parents or siblings had a significantly higher risk of developing AD, and this tendency was observed for both BA and AR. These results are similar to previously reported data in Japan.^{15,17} Furthermore, the number of comorbid diseases showed a significant positive correlation with the number of family histories of allergic disease. These results suggest that a certain genetic background influences the onset and comorbidity of allergic diseases.

Subjects diagnosed with a certain allergic disease have a greater likelihood of developing other allergic diseases. Approximately one-third of children with severe AD were reported to suffer from IgE-mediated FA as well.^{18,19} In addition, FA that developed at a young age increased the risk for AD, BA, and AR at 8 years of age⁷; in 9-11-year-old children, FA was highly associated with BA and AR.²⁰ Two prospective studies show that cow's milk allergy is associated with later development of either BA or AR.^{21,22}

We showed that FA significantly raised the risk of allergic disease comorbidity (AD, BA, and AR), especially AD, and critically increased the numbers of diseases with which it was comorbid. Furthermore, FA significantly lowered the age of onset for both AD and AR, and subsequently, AD significantly lowered the onset age of both BA and AR. These results suggest that FA and AD are closely associated and aggravate allergic march. Furthermore, Ricci *et al.* reported that the integrated management of AD decreases the likelihood that affected children would progress toward respiratory allergic disease.²³ Thus,

prompt management of AD and FA that develop in early infancy may be a successful method for preventing allergic march.

It is not yet understood whether FA or AD is first diagnosed and in which organ the sensitization to food initially occurs. Two possible mechanisms were reported as involved in the initial sensitization to food allergens: oral to gut mucosal exposure²⁴ and cutaneous exposure. Recent modern theories suggest that the most important factor that precipitates allergic march is an impaired epidermal barrier. There is a clear evidence of a relationship between filaggrin gene (FLG) mutations and AD. FLG also increased the risk for BA with AD, and the risk for AR with/without AD.²⁵ Moreover, the presence of an FLG mutation in infants with early onset food sensitization and AD increases the risk for BA.^{26,27} However, an association of an FLG mutation with risk for FA has not been reported. Further investigation is needed to elucidate a clearer relationship between FA and allergic march.

We showed that both improvement and recurrence of allergic diseases are commonly outgrown during adolescence. To prevent allergic symptoms until adulthood, it is particularly important to elucidate recurrence and onset factors. Based on our results, early onset of disease or being female increased the likelihood that allergic disease would improve. Xerosis, seasonal changes, and sweating were the most important factors that made symptoms difficult to alleviate. An appropriate treatment including management of these aggravating factors is important for preventing AD.

There are some limitations of the present study. First, it is doubtful whether students remembered their allergic histories correctly because it was a retrospective study. To help offset this limitation, we sent the interview sheets to the parents so students could ask their parents before answering. Second, FA may be over-diagnosed in the study because FA was defined as a doctor's diagnosis. Few institutions or hospitals in Japan used oral food challenge tests for diagnoses of FA 15-20 years ago; an FA diagnosis was usually made by a blood test. FA might instead reflect food sensitization rather than FA diagnosed by oral food challenge test. Finally, our study population focused on students at Osaka University. However, these students originated from areas throughout Japan (especially western Japan) and represented an average 18-year-old Japanese university student.

In conclusion, a dynamic change in allergic march was demonstrated in our study. It is important to clarify the clinical course of allergic diseases from infancy to adulthood. Our results suggest that AD comorbid with FA in early childhood plays an important role in subsequent development of allergic march. Early childhood is thought to be a key period for the prevention of allergic march, and adolescence is an

other key period for the prevention of recurrence. The prevention of recurrence would decrease allergic disease in adulthood. Further prospective studies using large cohorts are necessary to assess this issue.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1-3 are available online.

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