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RESEARCH ARTICLE

Retrospective survey for clinical course and aggravating factors of adolescent atopic dermatitis in two years' cohort study on first-year university students

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Abstract

Background: Recent epidemiological studies have revealed increased numbers of adolescent subjects with atopic dermatitis, most of who experienced chronic symptoms since childhood. However, the complete clinical nature of atopic dermatitis in Japanese adolescents is poorly understood. We conducted this study to accumulate knowledge of factors contributing to protracted atopic dermatitis symptoms in adolescent subjects to avoid an unfavorable clinical outcome in these patients.

Methods: On 2013 and 2014, first-year students at our university answered a retrospective self-questionnaire about their demographic characteristics and past history of allergies. Answers from 6105 respondents were analyzed. Subjects with atopic dermatitis were divided into four groups according to their clinical courses, and factors potentially influencing their clinical courses were identified.

Results: Nearly 16% of the students had a history of diagnosed atopic dermatitis, many of who had experienced symptoms since childhood (protracted course). Other respondents had experienced remission (32%), adolescent onset (14%), or recurrence (6%). Logistic regression analysis found that psychological stress and air dryness were apparent exacerbating factors that increased the risk of the protracted, recurrent, and adolescence courses. Furthermore, sleep loss, house dust, pollen, high temperature, and sweat were the aggravating factors associated with the protracted course alone.

Conclusions: We found that a high proportion of Japanese adolescent subjects with atopic dermatitis had experienced protracted symptoms and further identified factors that may have led to this unfavorable course. We expect that limiting these factors in this population might alleviate the subjects' chronic symptoms.

KEYWORDS
adolescent, allergy, atopic dermatitis, exacerbating factor, prevalence

1 | INTRODUCTION

Lifestyle and an individual's environment change over time, and these changes may affect the natural course of allergic diseases, such as atopic dermatitis (AD). Previous epidemiological studies regarding atopic dermatitis have demonstrated the prevalence of this disease. Williams et al.[1] conducted a worldwide survey of children (ages 6–7 and 13–14) to investigate the sequential change in prevalence of eczema and found regional differences. Particularly, the regional difference in eczema prevalence in 13–14-year-old children showed a gap between developed and developing countries, while an increasing prevalence of eczema in 6–7-year-old children was found in most countries.[1] The number of Japanese eczema patients aged 15 years old or younger is increasing yearly.[2] Risk factors related to onset of Japanese AD were family history of AD, complications due to a preceding food allergy, constipation, and hypohidrosis.[3,4] On the other hand, factors related to spontaneous remission were gender (female), seasonal changes in symptoms, and regular intake of lactic acid bacteria.[3,4] One serious concern surfacing recently was that many adult and adolescent patients do not experience relief of their skin symptoms and have suffered from the disease since childhood.[3–6] We should account for the fact that AD occurs over a wide range of ages and is often exacerbated by specific factors according to age.[7] Therefore, age-dependent AD prevalence corresponding to exacerbating factors has important implications in determining a way to prevent disease aggravation and prolongation of the clinical course. Mortz et al.[8] conducted a survey on an adult cohort (28 and 29 years old) in Odense, Denmark to investigate the prevalence, persistence, and related exacerbating factors and found that important factors included a history of hand eczema or allergic rhinitis before age 14 or AD onset before 2 years old. Thus, understanding both the disease prevalence by age and how these factors change from childhood to adulthood are important for resolving this refractory and protracted disease. To this end, we conducted surveys of college freshman to better understand the nature of adolescent allergic diseases. Here, we report the factors contributing to protracted AD by analyzing data collected in the past 2 years.

2 | MATERIALS AND METHODS

2.1 | Study population and questionnaire sheet

This study adhered fundamentally to our previous study[4] but was performed with a modified questionnaire and over a different period of time. On 2013 and 2014, first-year students (6839) at Osaka University were administered questionnaires consisting of questions regarding medical histories of allergic diseases (atopic dermatitis [AD], bronchial asthma [BA], food allergy [FA], and allergic rhinitis [AR]), family histories of allergic diseases, the clinical course of each disease (age of onset, improvement, and recurrence), and potential aggravating factors. The answer sheets were brought to an annual medical checkup for new students. Complete responses from 6105 students were analyzed as described below. All students with atopic dermatitis received a clinical examination by a dermatology specialist. Among students with atopic dermatitis who received an examination, disease severity and frequency of psychological stress were scored using SCORing Atopic Dermatitis (SCORAD) by choosing from a simple list of responses (none, sometimes, often, and always).

2.2 | Definition of allergic disease in personal histories

Personal histories of allergic diseases and inspection of skin by a dermatologist were considered during this study. Personal histories of AD, BA, and AR were based on a doctor's diagnosis at any time of the student's life from birth to the present. The time of the most recent symptom(s) was reported as the age of improvement and/or recurrence.

2.3 | Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21.0. The chi-square test was used for comparisons between categorical variables. Potentially aggravating factors were evaluated by odds ratios (OR) and 95% confidence

TABLE 1 Demographic and clinical data of study subjects

	N (%)	Male (%)	Female (%)	*p* value
Total	6105	4138 (67.78[a])	1967 (32.22[a])	
Atopic dermatitis	971 (15.9[a])	681 (16.5[b])	290 (14.7[b])	.087
Bronchial asthma	706 (11.6[a])	528 (12.8[b])	178 (9.0[b])	<.001
Allergic rhinitis	2181 (35.7[a])	1591 (38.4[b])	590 (30.0[b])	<.001
Food allergy	451 (7.4[a])	315 (7.6[b])	136 (6.9[b])	.330
No allergic diseases	3241 (53.1[a])	2073 (50.1[b])	1168 (59.4[b])	<.001

Note: p values are given by chi-square test.

[a]Per total subjects ($n = 6105$).

[b]Per total number of each gender.

intervals (CI) with multivariate logistic regression after controlling simultaneously for potential confounders. Correlation coefficients were determined using Spearman's rank correlation test. In all analyses, $p < .05$ indicated statistical significance.

TABLE 2 Breakdown of subjects with atopic dermatitis

Demographic factor	N = 971
Age (18 years old/ 19 years old)	671/300 (69.1%/30.9%)
Male/Female	681/290 (70.1%/29.9%)
Age of onset (years old)	Median value 2 (IQR: 0, 5)
Age of disease remission (years old)	Median value 7 (IQR: 4, 12)
Age of recurrence (years old)	Median value 16 (IQR: 13, 17)
Past history of bronchial asthma	266 (27.4%)
Past history of allergic rhinitis	570 (58.7%)
Past history of food allergy	296 (30.5%)

Abbreviation: IQR: interquartile range.

3 | RESULTS

3.1 | Summary of clinical and demographic data

Table 1 summarizes the clinical and demographic data collected from all study subjects (n = 6105). More males (67.78%) than females (32.22%) participated in our study (Table 1). Data regarding history of allergic disease complications in subjects with a history of AD are shown in Table 2. The median age of disease onset, remission, and recurrence was 2, 7, and, 16 years, respectively (Table 2). Complications of BA, AR, and FA were reported in 27.4%, 58.7%, and 30.5% of the subjects, respectively, indicating the presence of an allergic march in many of the participants (Table 2). The natural clinical course of patients with AD, AR, or BA are summarized in Figure 1. As with our previous report, the peak of disease onset age was lower in patients with AD, followed by BA and AR in descending order (Figure 1, Table 2, Tables S1 and S2). Regarding the peak age

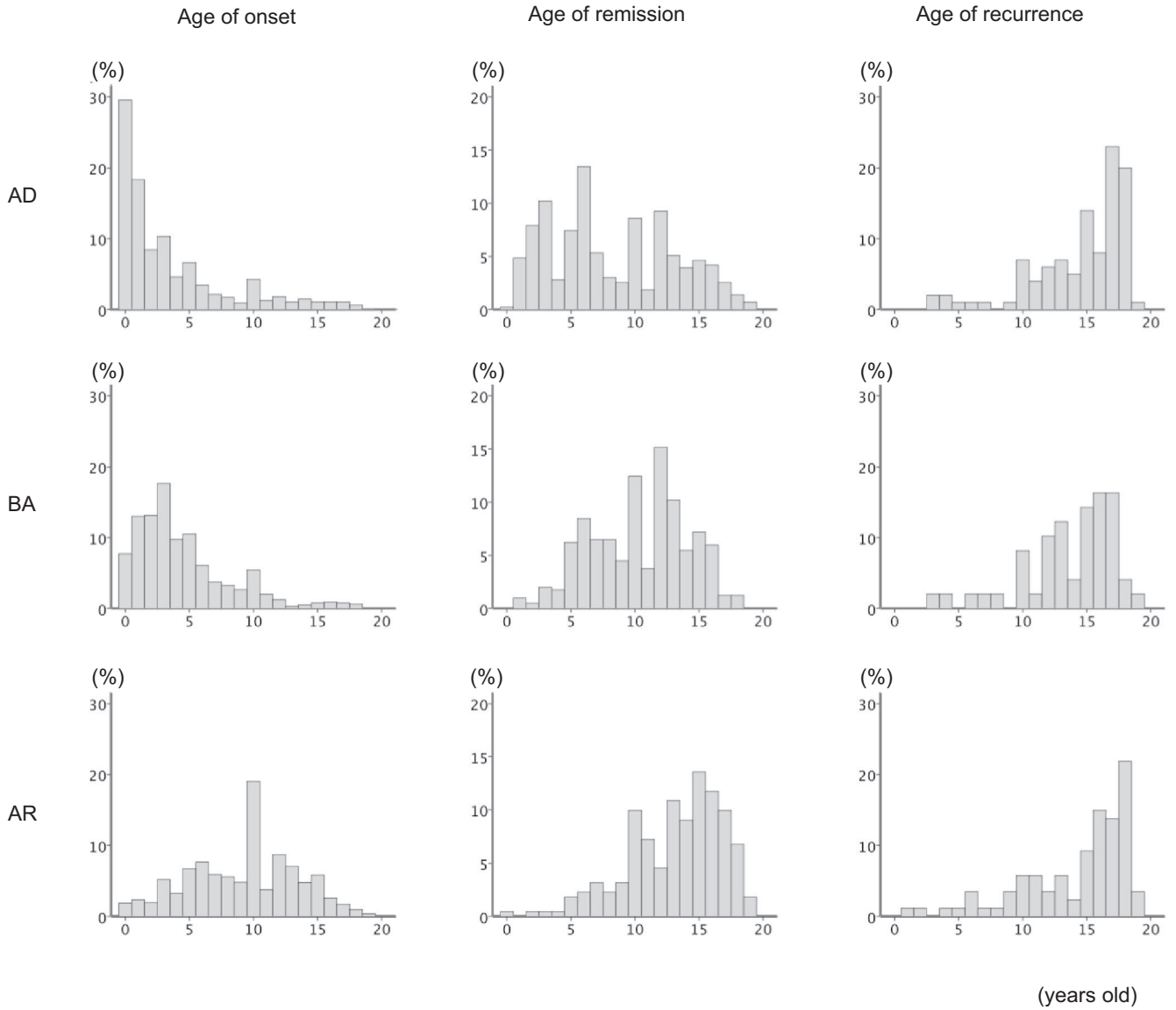

FIGURE 1 Natural clinical courses of allergic diseases identified in this study. Disease onset, remission, and recurrence are summarized according to atopic dermatitis (AD), bronchial asthma (BA), and allergic rhinitis (AR)

TABLE 3 Clinical courses of adolescent atopic dermatitis sorted by age of onset

Infantile phase	Childhood phase	Juvenile phase	Adolescent phase			Number of patients	%(/total)
0 years	1–6 years	7–9 years	10–12 years	13–15 years	16–19 years		
Start of AD in infantile phase						262	30.4
■	■	■	■	■	■	126	14.5
■	■	■	■	■		10	1.2
■	■	■	■		■	4	0.5
■	■	■	■			13	1.5
■	■	■		■	■	5	0.6
■	■	■		■	■	4	0.5
■	■	■		■		9	1
■	■		■	■	■	4	0.5
■	■		■	■	■	4	0.5
■	■		■	■	■	6	0.7
■	■		■	■		76	8.8
■	■		■		■	1	0.1
Start of AD in childhood phase						445	51.3
	■	■	■	■	■	264	30.4
	■	■	■	■		16	1.8
	■	■	■		■	1	0.1
	■	■	■			49	5.7
	■	■		■	■	1	0.1
	■	■		■	■	1	0.1
	■	■		■		17	2
	■		■	■	■	5	0.6
	■		■	■	■	5	0.6
	■		■	■	■	9	1
	■		■	■		77	8.9
Start of AD in juvenile phase						42	4.8
		■	■	■	■	34	3.9
		■	■	■		4	0.5
		■	■		■	1	0.1
		■	■			1	0.1
		■		■	■	2	0.2
Start of AD in adolescent phase						118	13.6
			■	■	■	50	5.8
			■	■		7	0.8
			■		■	1	0.1
			■			4	0.5
				■	■	32	3.7
				■		1	0.1
					■	23	2.7

Note: Columns filled with gray indicate the duration of symptoms.

of recurrence, all three allergic diseases presented a peak during late adolescence (Figure 1, Table 2, Tables S1 and S2).

3.2 | Characterization of clinical courses in adolescents with AD

To better understand the different clinical courses of AD in adolescents, we summarized their data by age of onset, remission, and recurrence (Table 3). First, we sorted the subjects by their age of AD onset and found that the number of participants with infantile, childhood, juvenile, or adolescent AD onset was 30.4%, 51.3%, 4.8%, and 13.6%, respectively (Table 3). Based on remission and recurrence information, we also divided the subjects into one of four types of clinical courses: 1) Remission: Infantile/juvenile onset subjects with complete remission (31.64%); 2) Protracted: Infantile/juvenile onset subjects without spontaneous remission (48.96%); 3) Recurrence: Infantile/juvenile onset patients who experienced disease recurrence

after spontaneous remission (5.89%); and 4) Adolescence: subjects who experienced adolescent onset of AD (13.51%; Figure 2, Table S3).

3.3 | Exacerbating factors influencing the natural clinical course of AD

To investigate the factors contributing to an intractable clinical course of AD, we analyzed their prevalence in our subjects and have summarized selected factors in descending order (Figure 3A). Exacerbating factors were determined by referring to the Japanese Guideline for Atopic Dermatitis.[7] Air dryness and sweat, known to cause dry skin and pruritus, respectively, were the most common answers. Next, we categorized the exacerbating factors by clinical course (Figure 3B). Among those who had recurrence, psychological stress and sleep loss were the prominent exacerbating factors. Autumn and cigarette smoke were the characteristic exacerbating factors for those in both the protracted and adolescence groups. Food and exercise were relatively frequent exacerbating factors in the remission and adolescence groups, respectively.

Furthermore, to find risk factors predisposing toward symptomatic AD, we focused on the aggravating factor(s) and performed linear regression analysis between the remission course and symptomatic courses (protracted, recurrence, and adolescence; Figure 4). The results are shown as a forest plot in Figure 4, comparing each of the three types of symptomatic clinical courses (protracted, recurrence, and adolescence) to the remission course separately.

Evident exacerbating factors predisposing toward a protracted course were psychological stress, sleep loss, house dust, pollen, temperature, sweat, and air dryness. Furthermore, evident exacerbating factors for recurrence type were psychological stress, pollen, and air dryness. Psychological stress and air dryness were the evident exacerbating factors promoting the adolescence course. In contrast, subjects who listed "food" as an exacerbating factor had a significantly low risk of protracted or adolescence course ($p = .01$ and $p = .002$, respectively; Figure 4, Table S4).

3.4 | Role of psychological stress in adolescent AD

Because psychological stress had the highest impact on the clinical course of adolescent AD (Figure 4), we attempted to identify the specific causes of this stress in subjects with AD, BA, and AR. It was noteworthy that subjects with AD considered both the effort of medication usage and AD symptoms as major sources of psychological stress (Figure 5). With regard to other two diseases, symptoms and limitation in daily life such as exercise limitation and detrimental to study cause psychological stress. Compared to other allergic diseases, features of stressor were distinctive in AD subjects and might be related to skin symptom (Figure 5). Thus, we also assessed the frequency of psychological stress in these patients but did not observe a significant correlation to their disease severity by SCORAD scores ($r = .053$, Spearman's rank correlation coefficient; Figure 6).

4 | DISCUSSION

In this study, we retrospectively evaluated the natural clinical course of AD in 6105 university students and assessed possible factors influencing the courses of AD in this population.

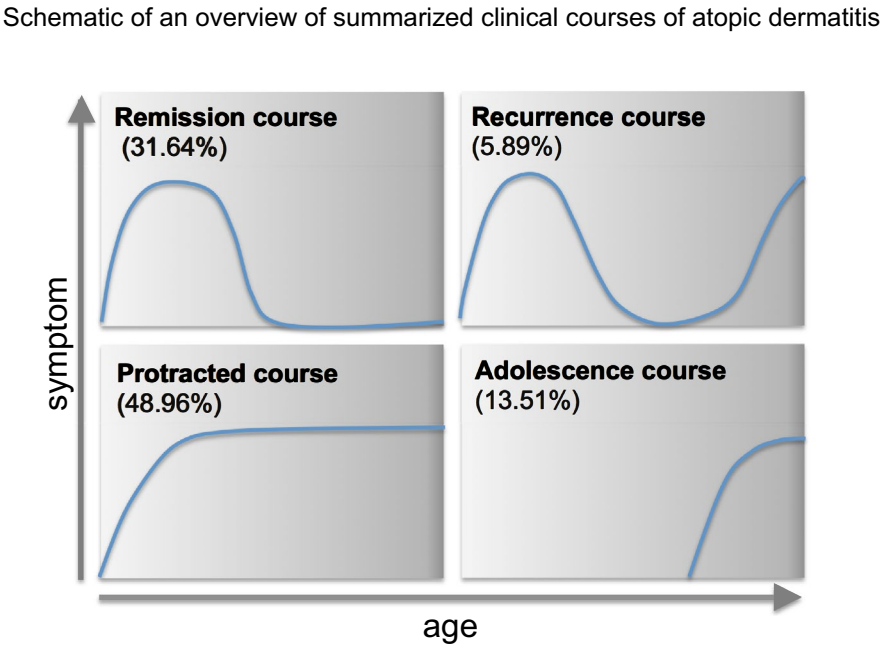

FIGURE 2 Schematic of an overview of summarized clinical courses based on the Table 3, and Table S3

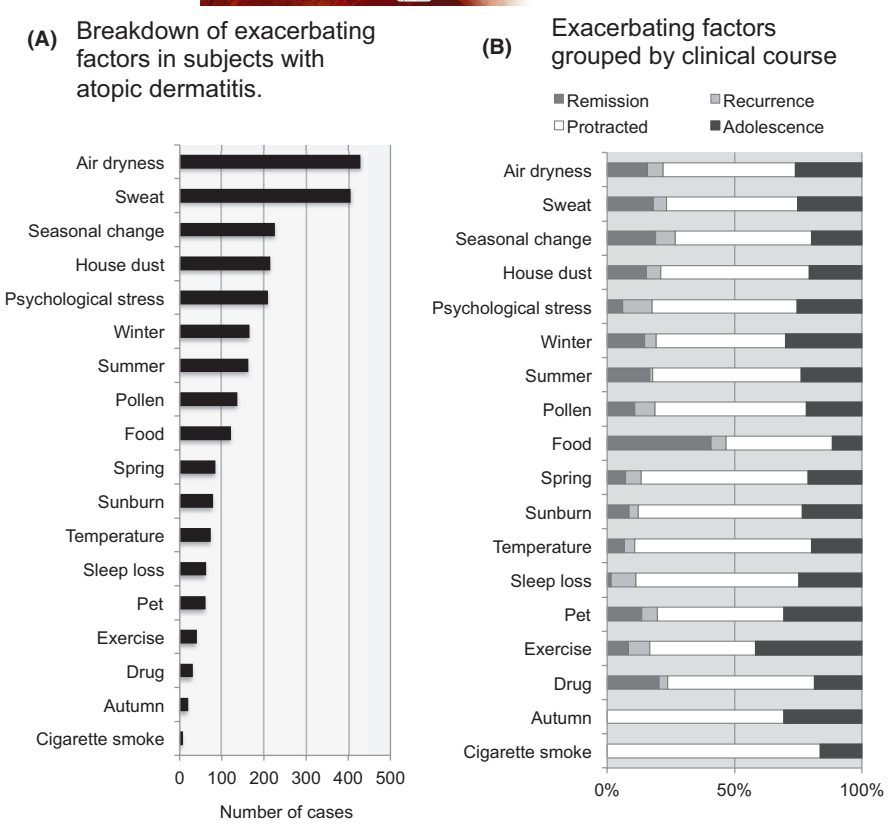

FIGURE 3 Breakdown of exacerbating factors in subjects with atopic dermatitis. Responses are represented as the total (A: left) or are grouped by disease type (remission, protracted, recurrence, or adolescence; B: right). X-axis indicates the number of cases

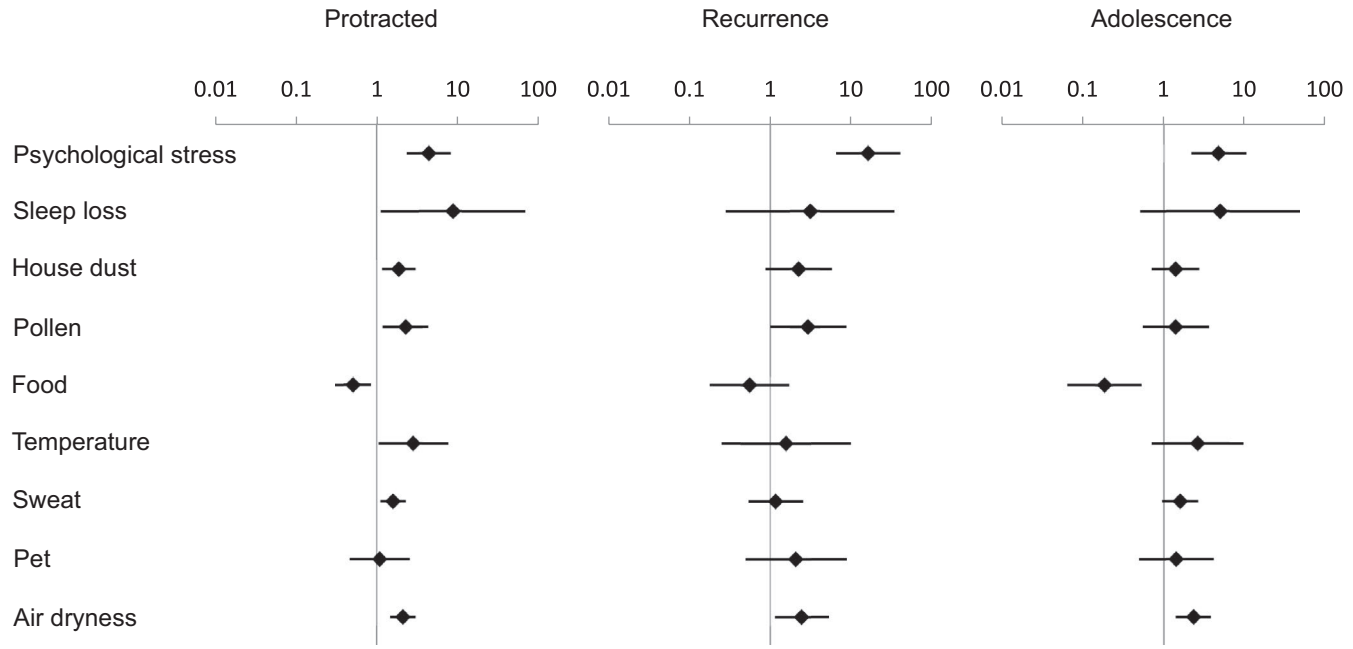

FIGURE 4 Relative odds ratio with 95% confidence interval for the protracted, recurrence, or adolescent-onset clinical course was calculated against the remission clinical course

Approximately 16% of the students had been diagnosed with AD, many of which experienced several AD-related complications, such as asthma, rhinitis, and food allergy, a phenomenon we had observed in a previous study.[4] Nearly half the AD subjects suffered from protracted symptoms, which often impairs patients' quality of life and work/classroom productivity.[9,10] Thus, identifying the exacerbating factors of AD and those that influence its clinical course is important for the successful management of AD symptoms.

The study cohort included university students but not patients who visited hospital. Thus, our cohort included subjects without allergic diseases. To date, there have been few surveys of lifetime AD prevalence in a general population of university students. In Spain,

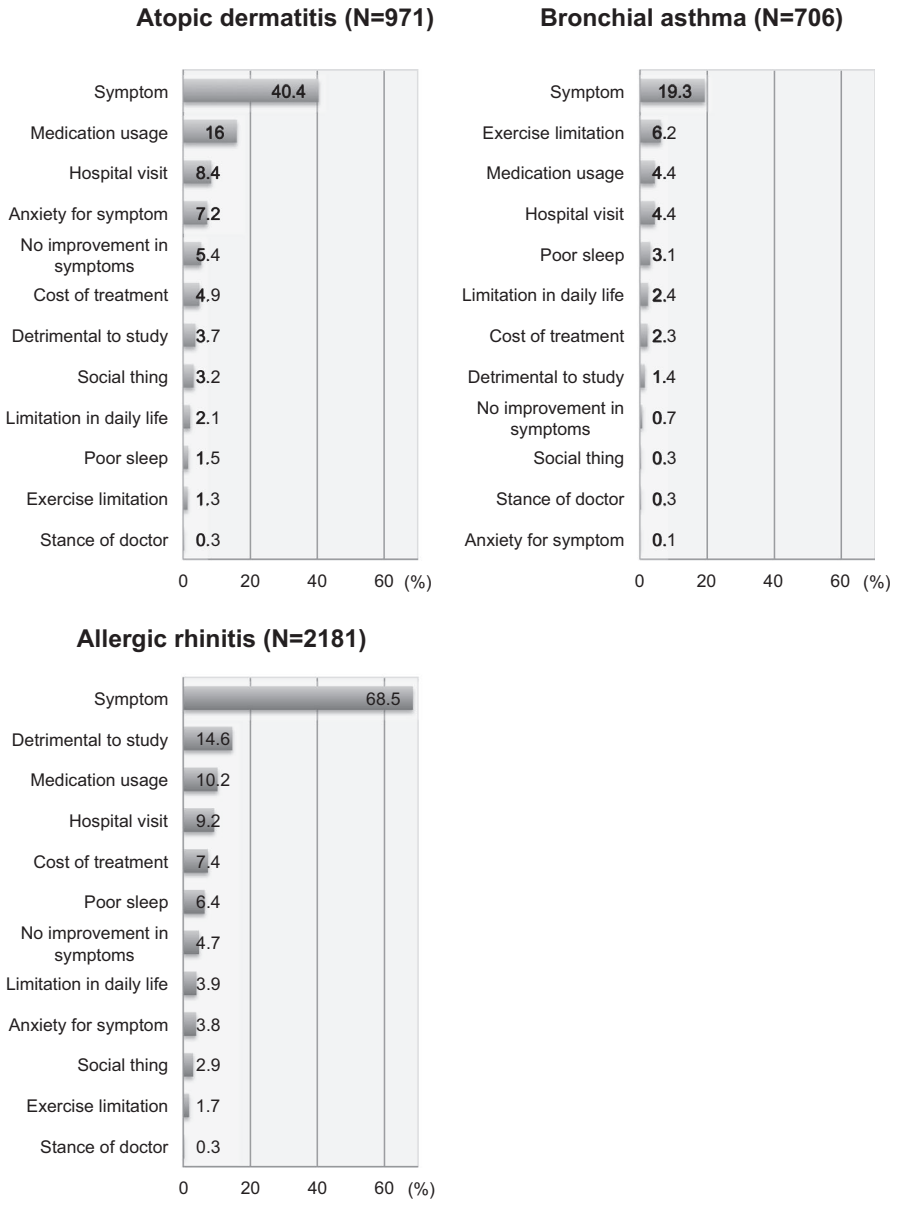

FIGURE 5 Sources of psychological stress in subjects with atopic dermatitis, bronchial asthma, and allergic rhinitis. X-axis indicates the percentage of total number of cases.

lifetime prevalence within age groups of 14–15 and 24–26 years old was 13.5% and 15.9%, respectively.[11] Incidence of AD in Danish adolescents (15 years old) was 20.4%.[12] In a population-based cohort study of German adolescents (16–20 years old) found that the probability of the incidence of AD was 21.4%.[13] In light of this evidence, the incidence of AD diagnosis in our survey was similar to that in previous reports. Previous reports of adult AD also found that many adult patients have experienced AD symptoms since infantile/childhood.[3,5,6,14–17] Nishioka et al.[15] further investigated Japanese adult clinical AD to determine the patients' current status and ongoing clinical course and found that 67% of the patients (mean age: 26.2 years old) had suffered from persistent AD symptoms since infancy or early childhood (0–4 years old). Regarding age-related clinical manifestations in these patients, skin symptoms began to spread widely throughout the body after puberty, and serum concentration of IgE increased as the disease duration prolonged.[15] Garmhausen et al.[6] summarized the characterization of clinical adolescent and adult AD and clearly presented the distinct subgroups according to the natural clinical course of AD. Moreover, demographic and clinical manifestations related to the patients' age of onset were investigated, and several manifestations characteristic of adult-onset atopic dermatitis were identified.[6] Their report focused on changes in clinical manifestations with respect to onset age and disease duration, while we examined the differences between patients in various clinical course groups. Thus, we could not make a direct comparison between the two studies. We also focused on comparing the age of recurrence between different allergic diseases. This survey was conducted for first-year university students with psychological stress due to entrance examinations. Despite that situation, the number of 19 years old students with recurrence was apparently small compared with 18 years old students. The peak age of allergic disease recurrence in students was 17–18 years old. Therefore, we speculate that high school life might affect recurrence of allergic diseases in some way.

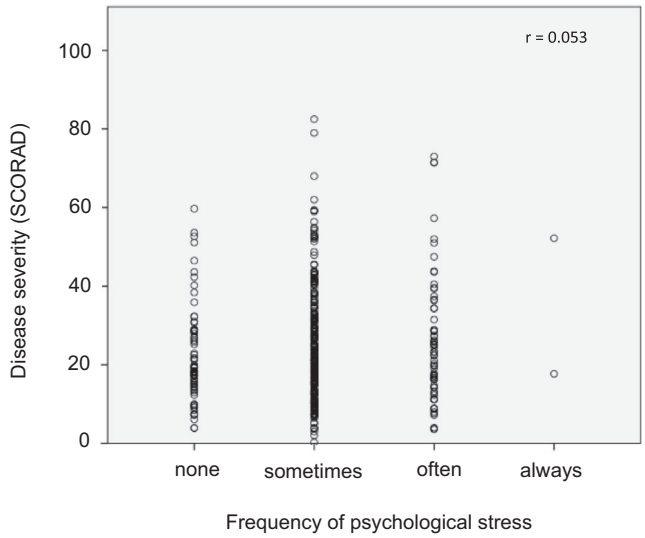

FIGURE 6 Relationship between disease severity (SCORAD score) and the self-reported frequency of psychological stress events experienced by the respondents. Spearman's rank correlation coefficient = .053

We aimed to identify appropriate preventive measures to minimize the occurrence of protracted AD symptoms and noted many possible exacerbating factors, such as psychological stress, house dust, pollen, temperature, sweat, and air dryness, all of which constituted a significant risk of protracted AD. One possible countermeasure to the patients' psychological stress might involve helping them develop effective coping mechanisms. The degree of psychological stress largely depends on one's interpretation of his or her circumstances and daily life events. The ability to cope with psychological stress varies among individuals, although a unique coping ability in subjects with AD involves negative itch-related cognitions,[18] an approach that could help prevent unfavorable clinical courses of AD in some patients. However, further studies are required to investigate the effectiveness of this technique.

Furthermore, subjects who considered food an exacerbating factor experienced significantly higher rates of AD remission. This result was unexpected result because food allergy is a frequent complication of childhood AD. In our previous study, food allergy-related comorbidity was the highest risk factor for the progression of allergic march, and we had concluded that AD associated with food allergy accelerates this progression.[4] We also found that AD with accompanying food allergy occurs earlier than AD alone. Moreover, the majority of infantile subjects outgrow AD,[4] which indicates the presence of food allergy could reflect the occurrence of remission in infantile AD patients.

Although we identified factors that potentially affect the natural clinical course of AD in adolescent subjects, there are limitations to this study. First, the accumulated data were derived from a limited cohort comprised of first-year students at our university. Second, data were collected via a retrospective self-questionnaire. Nevertheless, our study determined both the actual prevalence of AD and its complications, as well as provisional clues to improve the clinical course of AD in this population. We expect these results could lead to specific studies of exacerbating factors of AD and how the protracted clinical course can be prevented in AD patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MNT, MM, and MM performed statistical analysis and preparative work. HM wrote this manuscript. MNT and HM conceived the questionnaire. MNT, HM, and IK examined the skin manifestations. KYT organized the annual medical checkup for new students of our university. HI provided the statistical method. IK created an overview of this study.

DECLARATION SECTION

Approval of research protocol: Approved by the ethical committee of Osaka university. Approved ID 12003.

Informed Consent: Subjects were given veto power to answer the questionnaire.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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