

## Original Article

## Factors associated with the development of oral allergy syndrome: A retrospective questionnaire survey of Japanese university students



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## ARTICLE INFO

## Article history:

Received 8 October 2020

Received in revised form

11 January 2021

Accepted 4 February 2021

Available online 19 March 2021

## Keywords:

Awareness of OAS

Cross-sectional study

Oral allergy syndrome

Questionnaire survey

Risk factors

## Abbreviations:

AD, atopic dermatitis; AR, allergic rhinitis;

BA, bronchial asthma; FA, food allergy;

OAS, oral allergy syndrome; PFS, pollen food

allergy syndrome

## ABSTRACT

**Background:** Oral allergy syndrome (OAS) is an IgE-mediated food allergy. Ingestion of causative antigens leads to the development of local symptoms such as numbness of the oral mucosa in most cases and anaphylaxis in a few cases. The prevalence of OAS including in healthy people has not been investigated. Thus, we conducted a questionnaire survey of Japanese university students.

**Methods:** We conducted a cross-sectional study of 2688 first-year students using a questionnaire survey in marksheet format and examined the epidemiological characteristics of OAS.

**Results:** Only 2.7% of students were aware of the term “oral allergy syndrome”. A total of 143 (5.3%) students had OAS. There were significant associations between OAS and other allergic diseases including allergic rhinitis (AR) (OR: 3.8, 95% CI: 2.7–5.5), atopic dermatitis (AD) (OR: 4.6, 95%CI: 3.3–6.6), and bronchial asthma (BA) (OR: 3.0, 95%CI: 2.0–4.5). The onset age of OAS showed bimodal peaks at 0 and 10 years, and the latter peak coincided with the peak onset age of AR.

**Conclusions:** Awareness of OAS was low in our study, which will make it difficult to treat properly and prevent its development. This survey confirmed the association between OAS and other allergic diseases, especially AR, which suggests that OAS is involved in the allergic march. A novel finding was that sensitization to antigens for OAS occurred around the same time as sensitization to antigens for AR. These results will help medical professionals diagnose OAS and develop lifestyle guidelines to prevent OAS-related symptoms such as anaphylaxis.

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## Introduction

Oral allergy syndrome (OAS) is an IgE-mediated food allergy (FA) that mainly leads to oropharyngeal mucosal symptoms immediately after antigen intake.<sup>1</sup> The medical terms “oral allergy syndrome” is used by physicians, and appears as a medical term in the guidelines of the Japanese Society of School Health,<sup>2</sup> and in press reports. However, there is little information about how much this term is familiar to the general population.

Many allergens that induce OAS are easily inactivated by digestive enzymes; therefore, symptoms such as itch and numbness of the oral mucosa are often transient and localized. People

who suffer from OAS do not always visit medical institutions because they can avoid the onset of this condition by not ingesting the causative antigens or by thorough cooking of food.<sup>3</sup> Therefore, it is important to survey a group that includes subjects who have not visited a hospital to estimate the prevalence of OAS. However, previous reports have only included patients with an allergic disease, and a cross-sectional survey including healthy people has not been conducted. Here, we report the outcomes of a questionnaire survey regarding onset age and risk factors for OAS among Japanese university students.

## Methods

## Study participants

This cross-sectional study was conducted on first-year students at Osaka University, Japan in 2018. A questionnaire in marksheet format was sent to their homes and collected at the time of medical

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Peer review under responsibility of Japanese Society of Allergy.

examination. Responses were received from 3339 out of 3343 students and those of 2688 participants (1555 men and 1133 women) were analyzed: 22 and 629 students were excluded because they were older than 30 years and had missing data, respectively. Students over 30 years old were excluded from this study to reduce the impact of age-related lifestyle. The study protocol was approved by the Nagasaki University and Osaka University Institutional Review Board (approval no. 18122801 and 15476, respectively).

### Contents of the questionnaire

To avoid unclear or vague answer, the questionnaire had sent to the students' family homes, and the students were asked to answer the questionnaire with the help of their parents. The questionnaire asked about the student's age, gender, exacerbation factors, onset age of four allergic diseases (allergic rhinitis [AR], FAs including OAS, bronchial asthma [BA], and atopic dermatitis [AD]), family histories, awareness of OAS, and hand eczema. Excerpts from the questionnaire are shown in [Supplementary Figure 1](#).

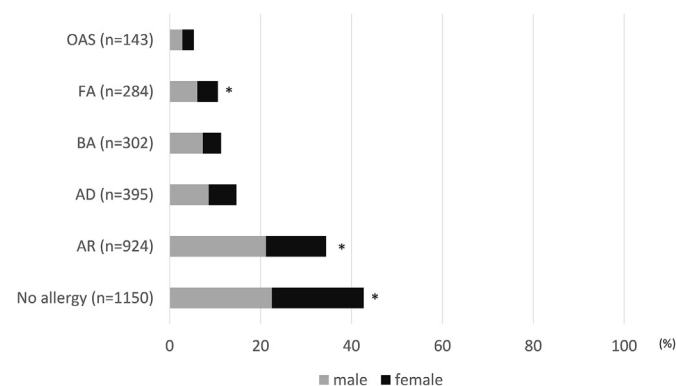
### Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 23 for Windows. Differences between genders were evaluated by the chi-square test. The relationship of OAS with each allergic disease and exacerbation factors were evaluated by calculating the OR and 95% CI in logistic-regression analysis. A P-value less than 0.05 was regarded as statistically significant.

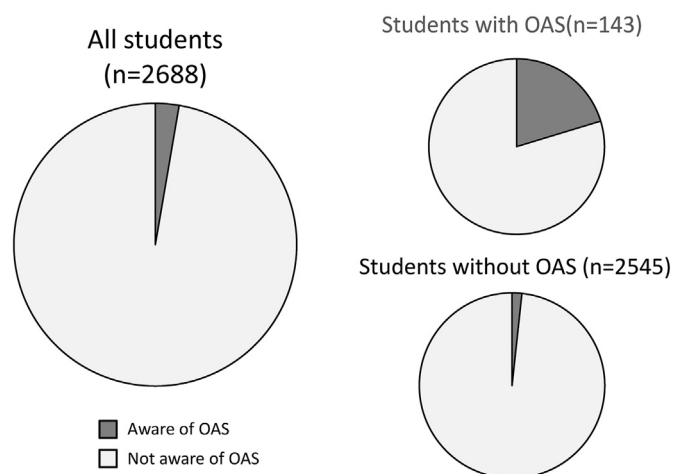
## Results

### Characteristics of the students

The mean age of first-year students was  $18.4 \pm 0.8$  years (mean [SD] 18.4 [0.8] years for males, and 18.3 [0.8] years for females). 10.5%, 34.3%, 14.6%, and 11.2% of students had FA, AR, AD, and BA, respectively, based on previous diagnoses by medical doctors. Students with FA were classified as having OAS if they had oral mucosal symptoms caused by antigen intake, and the prevalence was 5.3% ([Fig. 1](#)). The prevalence of OAS did not differ significantly by gender.



**Fig. 1.** Prevalence of allergic diseases (n = 2688). Multiple answers were allowed. The gray and black bars show prevalence of OAS in males and females, respectively. \* Significant difference according to gender (p < 0.05).



**Fig. 2.** Awareness of OAS in all students, students with and students without OAS. The gray and black areas show the proportion of students who were not aware of OAS, and those who aware of OAS, respectively.

### Awareness of OAS

We asked the students whether they were aware of the term “oral allergy syndrome” and calculated the percentage of students who were. In total, 2.7% of all students and 20.3% of students suffering from OAS were aware of the term “oral allergy syndrome”.

Awareness of this term was significantly higher among students with OAS than among students without OAS (p < 0.001) ([Fig. 2](#)). A history of AR, FA, or BA in a close relative was also a factor that increased the rate of awareness ([Table 1](#)).

### OAS antigens

Among causative foods of OAS, fruits were the most major cause (53.8%), followed by seafood (15.4%) and nuts (14.0%) (multiple answers allowed) ([Fig. 3](#)). Students with OAS caused by seafood were significantly more likely to have AD, while there was no significant association with hand eczema (date not shown).

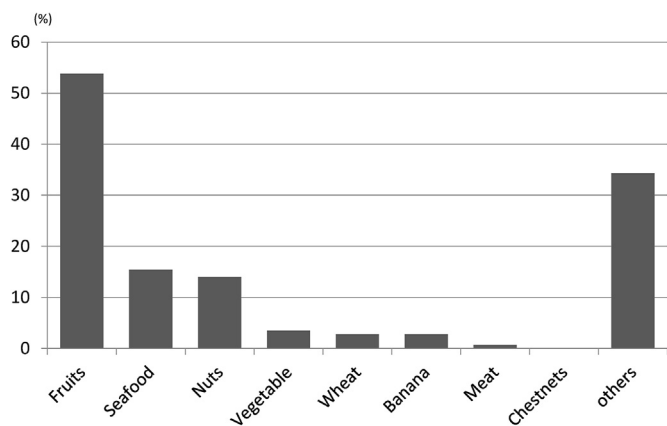
### Associations of allergic diseases and exacerbation factors with OAS

We analyzed the associations of allergic diseases and exacerbation factors with OAS using bimodal logistic regression analysis. The complication rates of OAS with AR, AD, and BA were 10.0% (OR: 3.84, 95%CI: 2.7–5.5), 14.9% (OR: 4.62, 95%CI: 3.25–6.57), and 12.3% (OR: 3.00, 95%CI: 2.02–4.46), respectively. There were significant associations between OAS and AD, AR, and BA. No common exacerbation factor in allergic diseases affected the incidence of OAS ([Fig. 4](#)).

**Table 1**  
Awareness of OAS among students with and without a family history of allergic diseases.

	With a family history n (%)	Without a family history n (%)	P-value
AR (n = 974)	44 (4.5)	29 (1.6)	<0.001
FA (n = 295)	20 (6.7)	53 (2.2)	<0.001
BA (n = 230)	13 (5.6)	60 (2.4)	0.004
AD (n = 363)	15 (4.1)	58 (2.4)	0.08

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



**Fig. 3.** Foods that cause OAS (n = 143). The vertical axis shows the percentage of OAS caused by different food.

### Onset age of OAS

Figure 5 shows the distribution of onset age of OAS, FA, and AR. The peak onset age of OAS was bimodal, with peaks at 0 and 10 years old. The former and latter peak onset age corresponded with the peak onset age of FA and AR, respectively. Furthermore, we examined factors related to the onset age of OAS such as gender, causative antigen, and comorbid allergic diseases (Fig. 6). The onset age of OAS caused by ingestion of fruits was significantly older than the onset age of OAS caused by the ingestion of other foods ( $p = 0.01$ ). The onset age of OAS was not associated with gender ( $p = 0.38$ ), or allergic diseases ( $p = 0.77$ ,  $p = 0.06$ , and  $p = 0.38$  for AR, AD, and BA, respectively) (Supplementary Figure 2).

### Discussion

OAS is an emerging allergic disorder worldwide. Epidemiological information is required to manage this social issue. The lack of

epidemiological studies of OAS among Japanese adolescent had made us to conduct this study. This study investigated the prevalence and risk factors of OAS in adolescent subjects by conducting a questionnaire survey.

Since many factors are involved in the development of OAS, the prevalence of OAS reported in the literature varies considerably.<sup>3</sup> In a study that targeted populations with or without allergies, the prevalence of OAS was 3.4%.<sup>4</sup> This is similar to the prevalence reported in our study (5.3%).

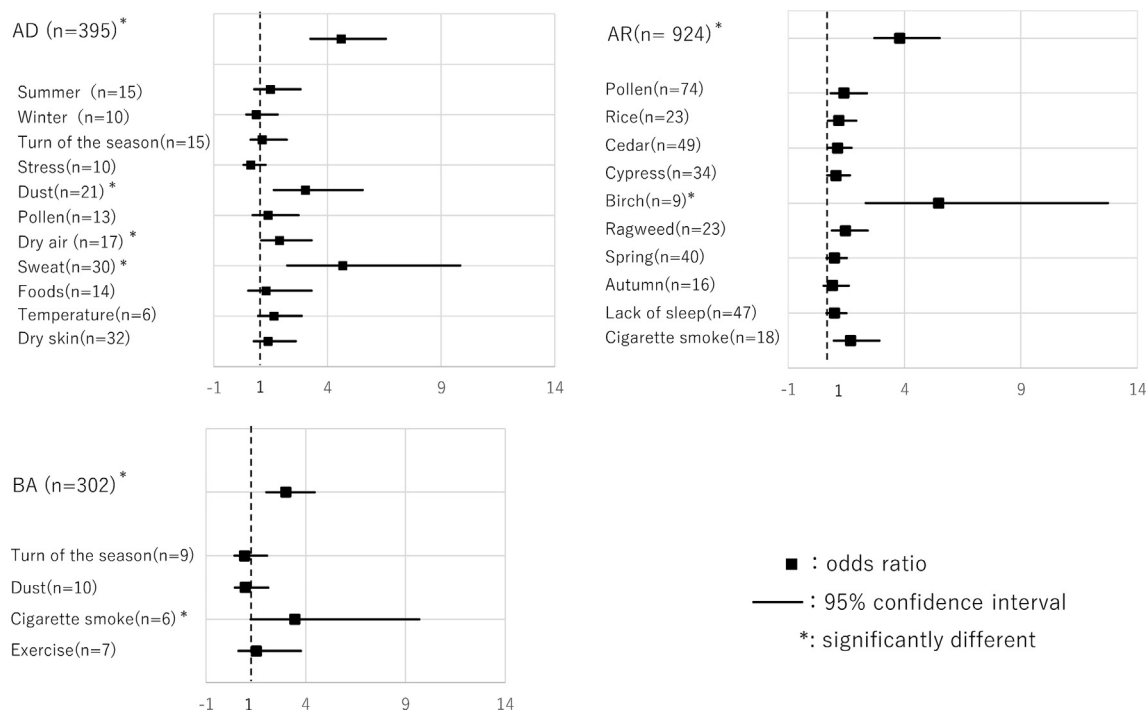
Although the impact of gender on the prevalence of OAS differs between previous reports, females are reportedly more likely to be affected by OAS than males.<sup>5</sup> Gender did not significantly influence the prevalence of OAS in the present study. Although a few studies have reported a gender difference in OAS prevalence, these studies found females were more likely to have visited a medical institution for allergic diseases.<sup>5–7</sup> In addition, the target age in these previous reports was much wider than in our study. Another study targeting a population, similar to that in our study reported no gender difference in the prevalence of OAS in university students.<sup>4</sup> Thus, it is possible that the reported gender difference in the prevalence of OAS is related to the age range of the study subjects in these studies.

AR was the most common allergic disease among people with OAS, and its complication rate was 65%. On the other hand, 10% of patients with AR had OAS, which was the lowest rate among allergic diseases. Hence, AR might be a risk factor of OAS, but not all subjects with AR develop OAS.

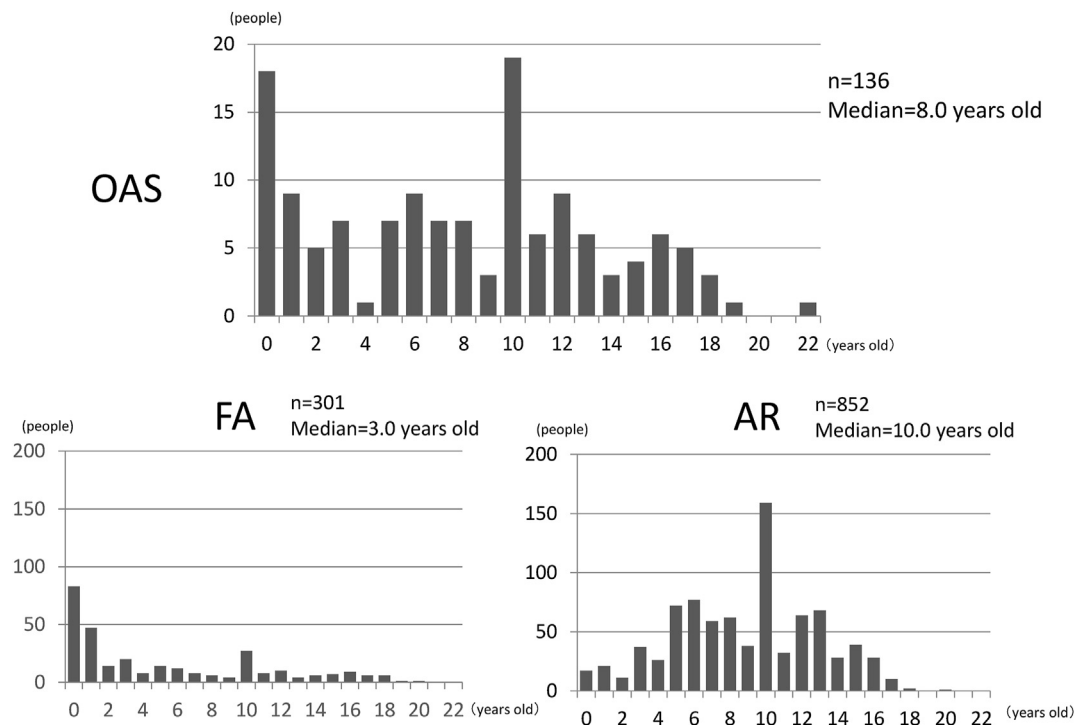
We also investigated awareness of the term “oral allergy syndrome” among the subjects. Only about 20% of subjects with OAS were aware of this term. This result indicates that the term “oral allergy syndrome” is a relatively new concept, and awareness of this term is low in the general population.

Next, we assessed other factors that influenced awareness of the term “oral allergy syndrome”. Comorbidity with allergic diseases or a family history of AR, FA, BA significantly increased the rate of awareness (Table 1).

As discussed above, patients with OAS are more likely to have AR. In particular, the frequency of pollen-food allergy syndrome



**Fig. 4.** Influence of allergic diseases (AD, AR, BA) and each exacerbation factor on the development of OAS.



**Fig. 5.** Distribution of onset ages of OAS (n = 136), FA (n = 301), and AR (n = 852). Median ages of onset were 8, 3, and 10 years for OAS, FA, and AR, respectively.

(PFS) is high among subjects with OAS. In the present study, fruits were the major causative food of OAS, followed by seafood. Seafood allergy is suggested to be caused by percutaneous sensitization, and is likely to arise in people with hand eczema or AD<sup>8</sup>. Many people with seafood allergy have oral mucinous symptoms. In the current study, OAS caused by seafood was significantly associated with AD ( $p < 0.001$ ). However, the number of subjects was too low to evaluate the statistical relationship with hand eczema. Further data are required to clarify this point.

A previous survey of Japanese subjects with OAS reported that they most commonly developed OAS in their 20s, with OAS onset occurring between 10 and 30 years old in 73% of subjects.<sup>9</sup> However, it is unclear when OAS patients are sensitized to allergens. It has been reported that sensitization to AR-related antigens plays a role in the pathogenesis of OAS. In other words, OAS likely develops after sensitization to pollen. In a previous questionnaire survey of children of 15 years or younger with AR in Osaka, Japan, more than 90% of them developed AR when they were under 10 years old age.<sup>10</sup> These results led us to speculate that OAS may develop after onset of AR. On the other hand, our survey found that the peak onset age of OAS was bimodal with peaks at 0 and 10 years, and the former peak and the latter peak coincided with the peak onset age of FA and AR, respectively. OAS is known to be one of the symptoms of FA. Thus, most subjects with a peak onset age at 0 years old in OAS might have their symptoms complicated by FA. The coincidence between the peak ages of onset of AR and OAS was unexpected, but coherent, and could only have been obtained by studying a population that included healthy people. Moreover, based on this result, two cases were considered, one in which OAS develops in close proximity to the onset of AR, and the other in which OAS develops independently of AR. The following three results (data not shown) also support this. First, the peak onset age of

AR was 10 years old among subjects with OAS. Next, among the students who developed AR at 10 years old, the peak onset age of OAS was also 10 years old. Last, among OAS subjects with an onset age of 10 years old, some did not have AR. We have no experimental data to explain why the peak of onset age of AR was 10 years old. The only thing that can be said with certainty about this data was that 10 years old was a critical time for the development of AR. Coincidentally, the WHO has defined 10 years old as the age of onset of puberty. The most epidemiological surveys are heavily influenced by birthplace and target age. Although our study also has some limitations, this survey suggests that AR and OAS develop simultaneously.

The number of patients with AR is gradually increasing and the decreasing onset age of AR is regarded as a problem.<sup>7</sup> This will lead to an increase in the number of patients with OAS and a decrease in the onset age of OAS. In contrast to AR, only patients can notice OAS symptoms. Thus, it is difficult to confirm the presence of OAS in children who cannot precisely describe their symptoms. It is important for healthcare professionals to ask about symptoms, in pediatric consultations. The epidemiological findings of the current study show the importance of increasing awareness of OAS.

#### Limitations

Our study has some limitations. First, the responses of the students may have been inexact because they sometimes depended on memories from more than 10 years ago.

Second, there was a bias in the birthplace of the students because this survey only included students at Osaka University. The prevalence of OAS varies between regions, particularly in the PFS. Unfortunately, we did not ask the students about their birthplace,

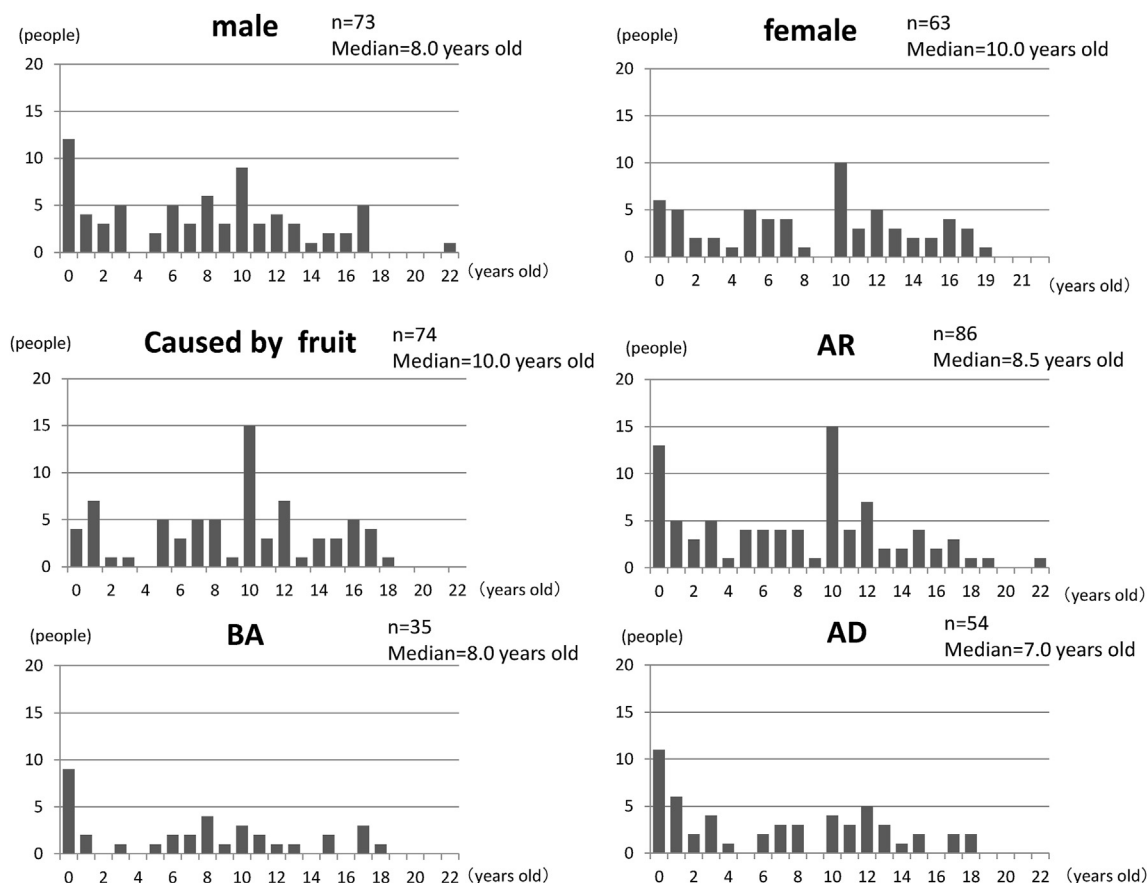


Fig. 6. Distribution of onset age of OAS according to gender and background factors. The median onset age is listed next to each factor.

and this information is important for interpreting the prevalence results.

## Conclusion

Our study revealed that awareness of OAS is low among university students. The number of OAS patients is expected to increase as the number of AR patients increases. Our results will help medical professionals diagnose OAS, improve understanding of OAS and assist in the development of lifestyle guidelines for the prevention of OAS-related symptoms.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2021.02.003>.

### Conflict of interest

MM received a research grant from Maruho. HM received research grant from Government of Japan Ministry of Health Labour and Welfare (Grant numbers: 201322007B), and grant from Japanese Society for Cutaneous Immunology and Allergy. The rest of the authors have no conflict of interest.

### Authors' contributions

MM analyzed the data, interpreted the results, drew the charts, and wrote the manuscript. MT interpreted the results, and revised the manuscript. YT, KA, and KAo performed statistical analyses, drew the charts, and revised the manuscript. KYT

formulated the study, collected data, and revised the manuscript. HM designed the study, interpreted the results, and revised the manuscript. All authors read and approved the final manuscript.

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