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Regional differences in the prevalence of oral allergy syndrome among Japanese children: A questionnaire-based survey

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Abstract

Background: Oral allergy syndrome (OAS) is characterized by an immediate allergic reaction that mainly or partially affects the oral mucosa, pharynx, or lips, and it is usually caused by ingesting fresh fruits or vegetables. Most patients with OAS also have allergic rhinitis due to pollen. As allergic rhinitis is increasingly prevalent in the Japanese population and the age at disease development is decreasing, morbidity associated with OAS among the younger population is likely to increase. However, there is little information about the prevalence of this disease among Japanese children, specifically the influences of residency in regions with different environments.

Objectives: To investigate the prevalence of OAS and seasonal allergic rhinitis (SAR) among Japanese children and evaluate the relationship between OAS and SAR.

Methods: We administered a questionnaire-based survey among children aged 7–15 years, living in 4 cities in central Japan.

Results: The questionnaires were administered to 4103 children and completed by 3365 (82.0%). Overall, 524 children (15.6%) reported OAS-like symptoms after ingesting fruits or vegetables. The prevalence of seasonal SAR and oral symptoms significantly differed among the 4 cities. The total prevalence of oral symptoms co-occurring with SAR was 24.4%, which was significantly higher than the prevalence of symptoms occurring without SAR (10.2%, $p < 0.001$).

Conclusion: Herein, oral symptoms were more likely to occur in patients with SAR than in those without SAR. The prevalence of SAR and food-induced oral symptoms significantly differed among the regions, suggesting they might be affected by regional differences in lifestyles and flora.

Key words: oral allergy syndrome, child, allergic rhinitis, prevalence, pollen-food allergy syndrome

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Introduction

Oral allergy syndrome (OAS) is an immunoglobulin (Ig) E-mediated immediate type of food allergy whose symptoms are mainly localized to the mucous membrane within the oral cavity.[1,2] Common causative foods associated with OAS are fresh fruits and vegetables.[3] Moreover, OAS is often complicated by pollinosis; OAS that develops after sensitization to pollen is called pollen-associated food allergy syndrome or pollen-food allergy syndrome.[4,5] Numerous studies have demonstrated a causative relationship between some pollen and OAS, for example, pollen of white birch and apples. Bet v 1, a pathogenesis-related protein (PR)-10 in birch pollen, has cross-allergenicity to Mal d 1, which is a PR-10 in apples.[6,7] Indeed, a study based in Austria has reported that approximately 75% of patients with birch pollinosis present OAS symptoms after the ingestion of apples.[8] Another prominent example involves mugwort pollen and celery.[9] Cross-reactivity between tomato fruit and Japanese cedar pollen has also been reported.[10]

There are regional differences in the prevalence of seasonal allergic rhinitis (SAR) among adults.[11] For instance, a questionnaire-based study of SAR prevalence in China showed a wide between-region variation in prevalence between adults[12] and children.[13] These differences are likely attributable to variations in environmental factors, such as climate and vegetation.[14]

As SAR affects the risk of OAS, the prevalence of OAS shows regional variation and is likely affected by environmental factors that influence SAR prevalence. For instance, OAS prevalence in Hyogo prefecture, Japan, is higher in regions abundant in Alnus sieboldiana trees than in other regions where this type of tree is rare.[15] However, there have been few studies on the prevalence of OAS among Japanese children and its between-region variation.[16,17] Therefore, the present study aimed to investigate the prevalence of OAS and SAR among Japanese children in regions with different climates and to examine the relationship between OAS and SAR. This is the first survey of SAR and OAS prevalence among children living in different prefectures in Japan.

Methods

Study design

We administered a structured questionnaire-based survey among school children aged 7-15 years in 4 cities in central Japan. The survey was administered between September 2015 and February 2016. Four cities in central Japan with different climatic characteristics were selected (**Figure 1**). Maebashi, in Gunma prefecture, is a city located at 108 m above sea level (asl), with approximately 1200 mm of annual rainfall and little snow in winter. Numata city, located approximately 30 km north of Maebashi, is set in a mountainous region at 493 m asl. Saku in Nagano prefecture is located in a mountainous region approximately 55 km west of Maebashi, at 683 m asl,

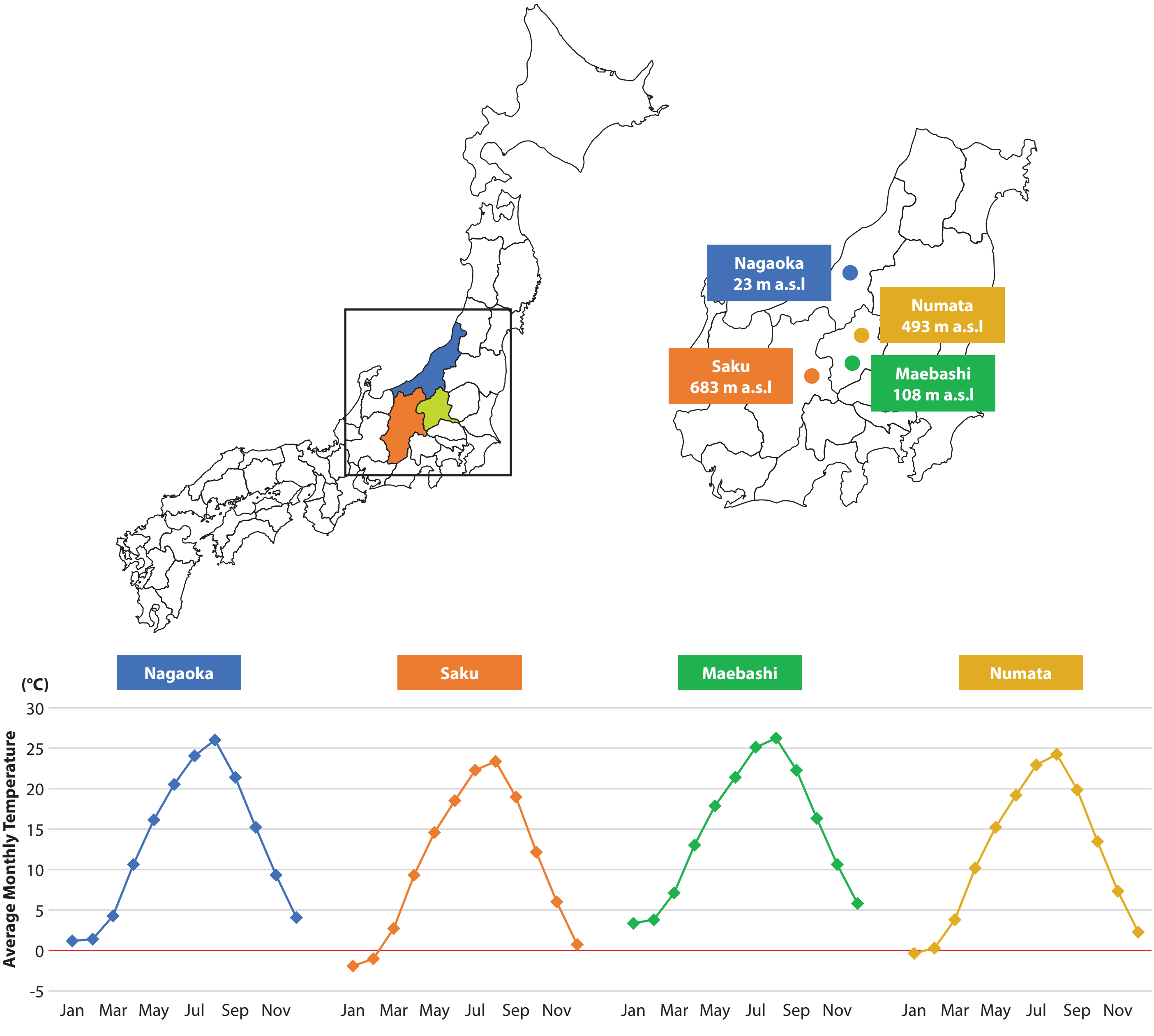

Figure 1. Profiles of the 4 cities in central Japan, including the altitude, average monthly temperature, and average monthly rainfall. Maebashi and Nagaoka are urban areas, whereas Saku and Numata are mountainous regions. asl, above sea level

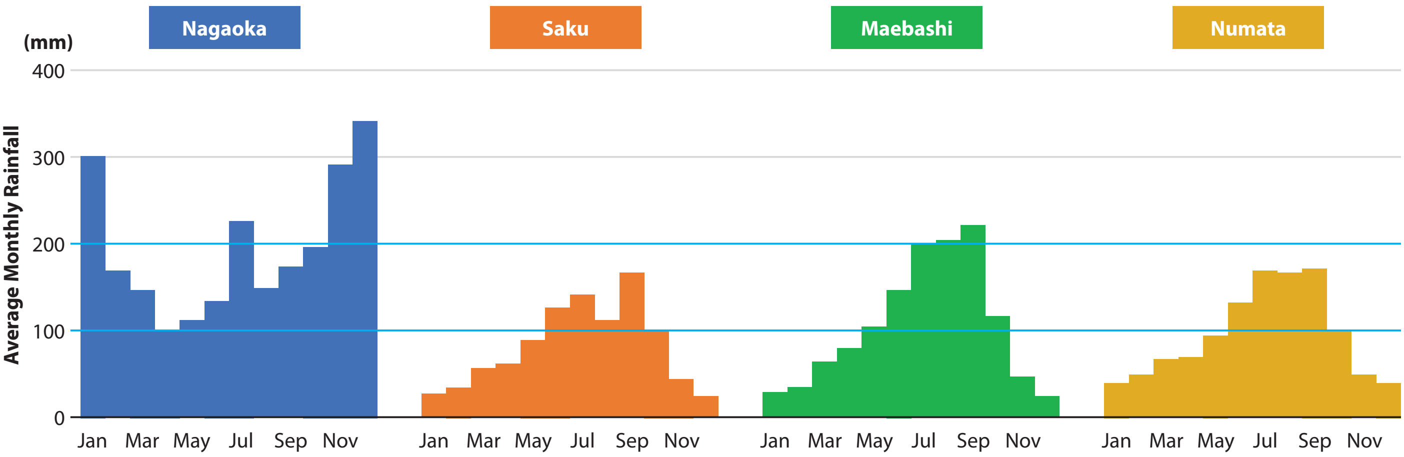

Figure 1. (Continued)

with winters colder than those in Numata. Nagaoka in Niigata prefecture is located approximately 120 km north of Maebashi and is a suburban city at 23 m asl, with the greatest annual snowfall among these four cities. Total forest areas in Maebashi, Numata, Nagaoka, and Saku are 7096, 33916, 34771, and 20165 hectares (ha), respectively. The coniferous forest areas in each city are 3,770 (53.1% of total forest area), 15728 (46.4%), 10862 (31.2%), and 14216 ha (70.5%), respectively. Forest of Japanese cedars and pine trees were only available in Saku and Nagaoka; Saku has 404 ha of Japanese cedars and 12803 ha of pine trees, while Nagaoka has 10663 ha and 171 ha, respectively. Among the 4 cities, only Saku has wild white birch trees. The burden seasons of the pollens of Japanese cedar, orchard grass, ragweed, and mugwort are similar in all the cities: February to April for Japanese cedar, May to August for orchard grass, and August to October for ragweed and mugwort. In each city, over 900 children from elementary schools and a junior high school participated in the study. Questionnaires were sent to 1 elementary and 1 junior high school in Maebashi, Numata, and Nagaoka, and to 3 elementary schools and 1 junior high school in Saku (Figure 1). Participation of 3 elementary schools was necessary to collect the questionnaires from ~600 students in Saku city, because the number of students in each elementary school in the city was small. Selection of schools was based on the recommendations of the Municipal Board of Education in each city. The questionnaire was distributed among all students, who were asked to complete it with their guardians at home, and it was subsequently collected by their teachers. The study protocol was approved by the Ethics Committee of Gunma University (#27-18). We gave prospective participants a document describing the study purpose, which informed them that participation was anonymous and that filling out a questionnaire would be considered to be indicative of consent to participation.

Questionnaire

We developed a questionnaire for this study that contained the following items:

1) What is your sex (boy or girl)?
2) What is your age?
3) Have you ever been diagnosed with seasonal allergic rhinitis (SAR) by an attending physician?
4) What kinds of pollen trigger your seasonal allergic rhinitis (multiple answers are permitted)?
5) Have you experienced any of the following symptoms after ingesting fruits or vegetables: itching; tingling; stinging; or numbness or swelling of the tongue, palate, mouth, ear, or throat? (If no, go to question 9.)
6) What type of fruit or vegetable causes any of the above symptoms (multiple answers are permitted)?
7) What kind of symptoms do you develop on the tongue, palate, lip, ear, or throat after ingestion of fruits or vegetables (multiple answers are permitted)?
8) What kind of symptoms, other than OAS-like symptoms, do you feel after ingesting fruits or vegetables?
9) Have you ever been diagnosed with any of the following allergic diseases by an attending physician: atopic dermatitis, bronchial asthma, perennial allergic rhinitis, or food allergy?

Statistical analysis

Chi-square tests were used to compare proportions between regions as categorical variables. The Cochran-Armitage test was used to evaluate age. Spearman correlation analysis was used to determine whether there were any correlations between the prevalence of SAR and oral symptoms. These statistical analyses were conducted using R version 3.2.2 revised (R Core Development Team).[18] Multiple logistic regression analysis was performed to calculate odds ratios (ORs) for the prevalence of oral symptoms between groups. These analyses were performed using SPSS statistics version 24 (IBM Corp.). The level of significance was set at $p < 0.05$ for all tests.

Results

Participants' characteristics

Overall, there were 4103 children aged 7-15 years across the included schools. The questionnaires were returned by 3365 children (82.0%) (**Table 1**). The number of responders was lower (72.3%) in Saku than in other cities. There were no differences between the cities in participants' sex and age. The mean prevalence of allergic diseases, atopic dermatitis (AD), bronchial asthma, perennial allergic rhinitis, and food allergy (FA) was 16.3%, 18.5%, 28.8%, and 6.0%, respectively (**Table 1**).

Table 1. Characteristics of children and allergic diseases in 4 Japanese cities

	Maebashi	Numata	Saku	Nagaoka	Total
Number of participants	1100	1046	931	1026	4103
Responders (%)	929 (84.5)	870 (83.2)	673 (72.3)	893 (87.0)	3365 (82.0)
Sex, male (%)	458 (49.4)	404 (46.6)	341 (50.7)	436 (49.0)	1639 (48.8)
Mean age (years)	11.0	11.0	11.1	10.9	11.0
Number of responders at each age, years old (%)					
7	101 (10.9)	104(12.0)	62 (9.2)	109 (12.2)	376 (11.2)
8	102 (11.0)	72 (8.3)	67 (10.0)	99 (11.1)	340 (10.1)
9	96 (10.3)	106 (12.2)	80 (11.9)	90 (10.1)	372 (11.1)
10	97 (10.4)	89 (10.2)	73 (10.8)	119 (13.3)	378 (11.2)
11	110 (11.8)	117 (13.4)	78 (11.6)	95 (10.6)	400 (11.9)
12	106 (11.4)	104 (12.0)	86 (12.8)	92 (10.3)	388 (11.5)
13	125 (13.5)	83 (9.5)	86 (12.8)	94 (10.5)	388 (11.5)
14	118 (12.7)	85 (9.8)	46 (6.8)	119 (13.3)	368 (10.9)
15	74 (8.0)	110 (12.6)	95 (14.1)	76 (8.5)	355 (10.5)
Atopic dermatitis (%)	165 (17.8)	116 (13.3) *	131 (19.5)	137 (15.3)	549 (16.3)
Bronchial asthma (%)	148 (15.9)	134 (15.4) *	170 (25.3) ***	170 (19.0)	622 (18.5)
Perennial allergic rhinitis (%)	277 (29.8)	265 (30.5)	167 (24.8)	260 (29.1)	969 (28.8)
Food allergy (%)	66 (7.1)	53 (6.1)	46 (6.8)	36 (4.0) *	201 (6.0)
Seasonal allergic rhinitis (%)	477 (51.3) ***	370 (42.5) **	231 (34.3) **	205 (23.0) ***	1283 (38.1)
Oral symptoms (%)	202 (21.7) ***	119 (13.7)	97 (14.4)	106 (11.9) *	524 (15.6)

Chi-square test: **p*-value < 0.05, ** *p*-value < 0.01, *** *p*-value < 0.001

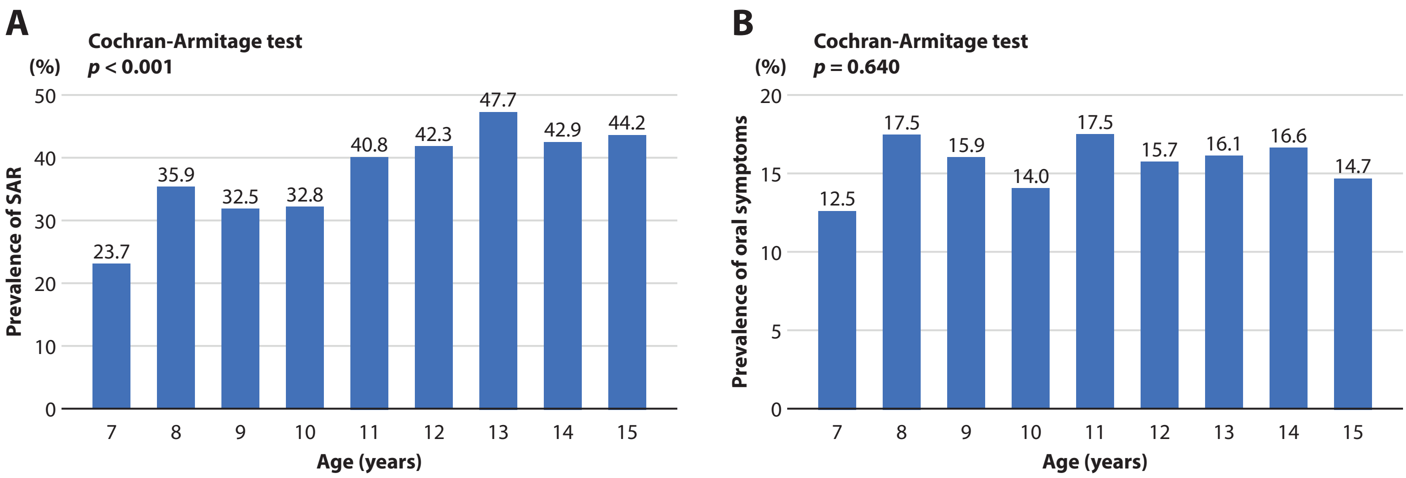

Figure 2. Prevalence of seasonal allergic rhinitis (SAR), oral symptoms, and other symptoms after ingesting fruits or vegetables
Age-stratified prevalence of SAR, which increases with age (Cochran-Armitage test, $p < 0.001$) (A). Age-stratified prevalence of oral symptoms, which remains approximately constant across age groups (Cochran-Armitage test, $p = 0.640$) (B). Frequencies of oral symptoms among 524 participants (C). Frequencies of symptoms other than those of the oral cavity (D).

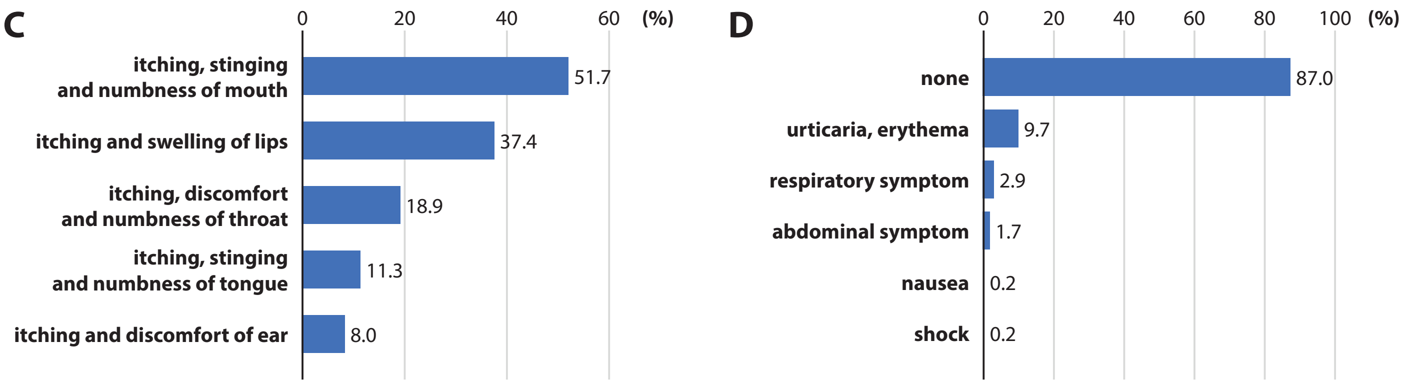

Figure 2. (Continued)

There were significant differences in the prevalence of AD in Numata city, asthma in Numata and Saku cities, and FA in Nagaoka (**Table 1**).

Seasonal allergic rhinitis

The average prevalence of SAR diagnosed by an attending physician was 38.1% (1283/3365). The prevalence of SAR increased with age (**Figure 2A**). The prevalence of SAR was the highest in Maebashi (51.3%) (**Table 1**), and it significantly differed among the cities. Fourteen different types of pollen were reported as triggers of SAR (**Table 2**). The most frequently reported cause of SAR was Japanese cedar pollen. Among children with SAR, 75.3% had been diagnosed as having SAR related to Japanese cedar (**Table 2**). Concurrently, white birch pollinosis, associated with Rosaceae fruit allergy, was diagnosed in only 1.0% of all children.

Oral allergy syndrome-like symptoms

The average prevalence of OAS-like symptoms (oral symptoms) after ingesting fruits or vegetables was 15.6% (524/3365) (**Table 1**). This prevalence was the highest in Maebashi (21.7%), and it differed significantly among the 4 cities (**Table 1**). There was no difference in the prevalence of oral symptoms between age groups (**Figure 2B**, p = 0.640). There were 39 different kinds of fruits and vegetables associated with oral symptoms. Fruits or vegetables frequently reported as being associated with OAS-like symptoms were kiwi fruit, pineapple, melon, Japanese yam, and watermelon. Of 524 children who reported oral symptoms, 341 (65%) reported at least 1 fruit or vegetable as a cause, 95 (18.1%) reported 2, and 44 (8.4%) reported 3 different foods as symptom triggers. The largest number of food triggers reported by 1 child was 8.

Children reported a range of oral symptoms after ingesting fruits or vegetables (**Figure 2C**). A combination of itching, tingling, stinging, and numbness of the mouth was the most frequently reported group of symptoms (51.7%). It is worth noting that most children reported itching inside the mouth. Indeed, 87.0% of the children who experienced oral symptoms reported experiencing exclusively oral symptoms (**Figure 2D**). Concurrently, other symptoms including skin manifestations, such as urticarial and erythematous rash, respiratory symptoms, and abdominal symptoms, were reported by 9.7%, 2.9%, and 1.7% of the surveyed children, respectively.

Table 2. Pollen types respondents with SAR were sensitized to

Pollen	Number (Total respondents with SAR 1283)	%
Japanese cedar	966	75.3
Ragweed	279	21.7
Rice	187	14.6
Cypress	184	14.3
Orchard grass	90	7.0
Sweet vernal grass	23	1.8
Wormwood	20	1.6
White birch	13	1.0
Weed	13	1.0
Timothy grass	12	0.9
Japanese alder	7	0.5
Pine tree	4	0.3
Wheat	4	0.3
Dandelion	2	0.2

Multiple answers were allowed.
Abbreviation: SAR, seasonal allergic rhinitis

Association between SAR and OAS

There was a correlation between the prevalence of SAR and oral symptoms in all regions (R = 0.848) (**Figure 3A**). Moreover, oral symptoms were more common among SAR-diagnosed than among non-SAR-diagnosed children (**Figure 3B**; p < 0.001). The sex- and city-adjusted OR for the prevalence of oral symptoms in SAR-diagnosed children was 2.751 (95% confidence interval: 2.259-3.351) (**Table 3**). A similar association was observed in each city (**Figure 3C**). The prevalence of oral symptoms was higher among children with than among those without SAR across all cities. The highest prevalence of oral symptoms among the SAR-diagnosed children was found in Maebashi (**Figure 3C**). For most foods, the ratio of oral symptoms in those with SAR to that in all participants was more than 50%, but Nagaimo yam and Mango showed lower ratios, indicating that the oral symptoms associated with those foods have a weaker association with allergic rhinitis.

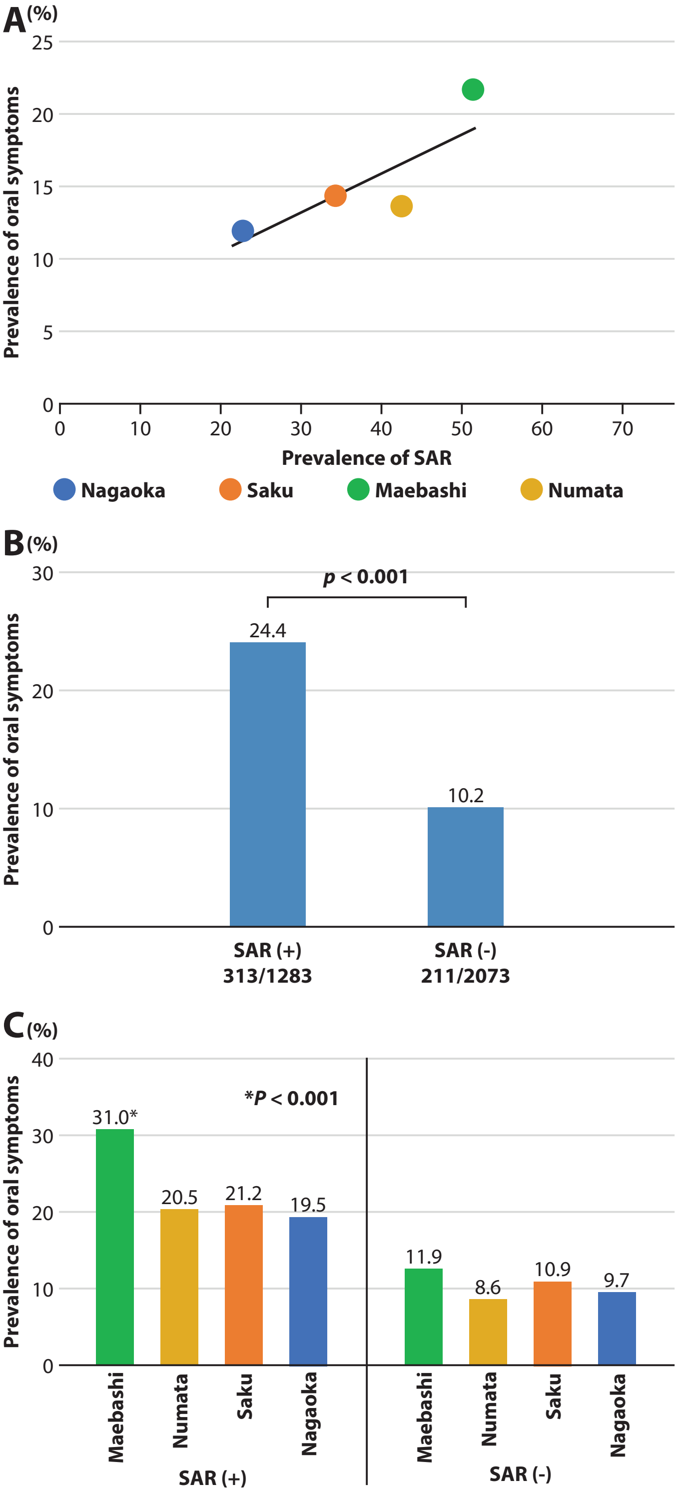

Figure 3. Correlation between seasonal allergic rhinitis (SAR) and oral symptoms
Correlation between the prevalence of SAR and oral symptoms across 4 cities. There is a linear association between the prevalence SAR and oral symptoms across 4 cities (Spearman's correlation analysis, $y = 0.3049x + 3.9053$, $R^2 = 0.7192$) (A). Comparison of the overall prevalence of oral symptoms in children with and without SAR (chi-square test, $p < 0.001$) (B). Prevalence of oral symptoms with or without SAR in different cities. Maebashi has a significantly higher prevalence of oral symptoms than that in other cities among children with SAR (chi-square test, $p < 0.001$) (C).

Table 3. Odds ratios and adjusted odds ratio for oral symptoms between children with and without seasonal allergic rhinitis

	Oral symptoms		Odds ratio	95% CI
	+	−		
SAR (+)	313 (24.4)	968 (75.5)	2.913	2.404-3.530
			*[2.751]	*[2.259-3.351]
SAR (−)	211 (10.2)	1858 (89.8)	1	
Sex				
male	224 (13.7)	1410 (86.3)	0.699	0.576-0.847
female	300 (17.5)	1415 (82.5)	1	
City				
Maebashi	202 (21.7)	727 (78.3)	1.402	1.067-1.840
Numata	119 (13.7)	751 (86.3)	0.908	0.671-1.228
Saku	97 (14.4)	576 (85.6)	1	
Nagaoka	106 (11.9)	787 (88.1)	0.846	0.630-1.136

Abbreviations: SAR, seasonal allergic rhinitis; CI, confidence interval
[ ]: adjusted data, *: data adjusted for sex and city

Discussion

The present study's results showed that oral symptoms were experienced by 15.6% of Japanese children aged 7-15 years. There was between-region variation in the prevalence of oral symptoms, even though the 4 cities are located relatively close to each other, indicating that the prevalence of oral symptoms is likely influenced by SAR and factors such as climate, vegetation, and living conditions.

The prevalence of SAR in the Japanese population was reported at 29.8% in 2008,[11] with an increase by 10% since 1998. The prevalence of SAR among adult populations in 4 regions with distinct climate in Japan, namely, Tokyo, Osaka, Hokkaido, and Okinawa, were reported at 33.8%, 27.4%, 18.8%, and 7.4%, respectively.[11] A study on the prevalence of allergic diseases among school children aged 7-12 years in a western district of Japan showed large differences in SAR prevalence; specifically, 10.0%, 8.7%, 19.7%, and 1.0% in Fukuoka, Nagasaki, Hyogo, and Okinawa, respectively.[19] In addition to the differences in the prevalence of a specific diagnosis, regional differences in pollen sensitization rates among adults and children have been reported in Japan.[20] The present study revealed large variations in SAR prevalence in 4 cities of central Japan, which have different climate characteristics even though they are in geographical proximity to each other.

Although OAS prevalence is expected to increase, there have been few studies on OAS prevalence in children residing in regions with distinct climate conditions. For example, the territory of Italy covers a significant stretch of land from north to south; OAS prevalence among children with SAR aged 4-18 years have been reported at 30.4%, 22.2%, and 16.9% in northern, central, and southern Italy, respectively.[21] In the present study, there was a close correlation between SAR and the prevalence of oral symptoms, suggesting that SAR might affect the development of oral symptoms in these regions.

As white birch, one of the best-known causes of OAS, occurs naturally only in Saku, we had expected that the prevalence of oral symptoms would be highest in this city. Contrary to our expectations, the prevalence of oral symptoms was the highest in Maebashi. Concurrently, most children with SAR included in the present study were affected by Japanese cedar pollinosis. Japanese cedar pollen has been shown to be molecularly associated with OAS triggered by tomatoes.[10] In the present study, oral symptoms related to tomato ingestion were reported by only 7% of respondents, which was a lower proportion than the proportions of respondents reporting symptoms triggered by kiwi (29.7%), pineapple (25.3%), and melon (16.4%). Similar tendencies have been previously reported in other surveys of the Japanese population.[16,17] However, cross-allergenicity has not been demonstrated between Japanese cedar pollen and these fruits. Therefore, the mechanism of comorbidity between Japanese cedar pollinosis and OAS remains unknown.

Previous studies have suggested accelerated expansion of sensitization to multiple allergens in patients already sensitized to one allergen.[22] Sensitization to Japanese cedar pollen might prime patients to become sensitized to other pollen types, such as birch pollen. However, as birch pollen or pollen from closely related trees is not as abundant locally as is Japanese cedar pollen, symptoms caused by these types of pollen might not be sufficient to be recognized. Future research should compare rates of sensitization to multiple types of pollen between participants with and those without Japanese cedar pollinosis.

This study has several limitations. First, this study was a questionnaire-based study. Second, sensitization was not directly tested. In non-SAR-diagnosed children, 10.2% reported OAS-symptoms. Currently, it is unclear whether those children are sensitized to food or pollens. They might be sensitized to neither food nor pollens, or they may be sensitized to both but have subclinical SAR-related symptoms. Future studies should involve sensitization testing such as IgE measurement or the skin prick test to validate these results. Third, the questionnaire intake season was September to February. This is not a typical season for pollinosis, which might have caused bias in participants' recalling symptoms of pollinosis. Therefore, it might affect the results in morbidity. Fourth, selection of schools was not randomized, which could cause bias in the study.

Conclusions

The present questionnaire-based study demonstrated that the prevalence of oral symptoms among children in central Japan was 15.8% and was closely correlated with SAR prevalence. This is the first report of regional differences in the prevalence of oral symptoms among Japanese children. These results can be a basis for further research on prevalence transition, pollen sensitization, and OAS. They can also support the development of prevention and therapeutic strategies for these diseases.

Conflicts of interest

The authors declare no conflict of interest in relation to this work.

Author contributions

TT designed the survey. MO and TT performed the survey and drafted the manuscript. MO, TT, YN, HY, KS, SY, and HA analyzed the data. All authors reviewed and edited the manuscript and approved the final version of the manuscript. All authors agree to be accountable for all aspects of this work and for any questions related to its accuracy or integrity.

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