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Original Article

The prevalence of oral symptoms caused by *Rosaceae* fruits and soybean consumption in children; a Japanese population-based survey

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PFS Pollen food Syndrome

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ABSTRACT

Background: Pollen food Syndrome (PFS) to *Rosaceae* fruits and soybean, related to Bet v 1 homologue sensitization has been reported increasingly throughout Japan, possibly due to the wide distribution of alder.

Methods: In 2015, we conducted a school-based questionnaire survey among two age groups; students in primary school (Years 1–2) and secondary school (Years 8–9) from each of the 47 prefectures of Japan. We analyzed the prevalence, demographic and clinical characteristics of children with oral symptoms to *Rosaceae* fruits/soybean; defined as oral symptoms occurring shortly after ingesting apple, peach, cherry or soybean. Additionally, we assessed the correlation between the prevalence and external data on alder sensitization rates by prefecture.

Results: Responses from 41,264 primary and 35,302 secondary school students were analyzed. The prevalence of oral symptoms to *Rosaceae* fruits/soybean was 0.99%, 95%CI: 0.89–1.09% and 2.75%, 95%CI: 2.59–2.93% among each age group, respectively. Children with oral symptoms were more likely to have parental and personal history of allergic disease compared to those without symptoms. Oral symptoms were experienced more often in children with severe spring allergic rhinitis or have both allergic rhinitis and wheeze. There was a strong correlation between the prevalence of oral symptoms and alder sensitization rates by prefecture among both age groups ($r = 0.63$, $p < 0.001$ and $r = 0.76$, $p < 0.001$, respectively).

Conclusions: Oral symptoms to *Rosaceae* fruits/soybean, which is suggestive of PFS was reported by 1–3% Japanese school children. It was associated with the geographic alder sensitization rate, supporting the underlying sensitization to Bet v 1.

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Introduction

Birch related Pollen Food Syndrome (PFS) is a class II food allergy most commonly caused by the cross reactivity between the major birch allergen Bet v 1, which belongs to the group of pathogenesis-related protein family number 10 (PR-10), and its

homologous proteins in various foods.^{1–3} The typical presentations are localized symptoms in the oral cavity such as itchiness and swelling upon ingestion, thus previously often referred to as oral allergy syndrome (OAS). Due to the sensitivity of Bet v 1 homologous food allergens to heat and proteases, triggers are mainly raw fruits of the *Rosaceae* family such as apple, peach and cherry,^{1,4} although Bet v 1 homologous proteins in hazelnut, celery, peanut and soybean may be more heat stable and occasionally cause systemic reactions.⁵

Birch-related PFS is a long known and common condition in areas such as Northern and Central Europe and North America, where birch is one of the most common causes of seasonal allergic

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rhinitis.^{6–8} A recent survey of UK adults aged 18–75 using a validated diagnostic questionnaire reported a prevalence of PFS at 2%, with the peak age of onset between 10-to-14-year-old.⁹ In Japan, although wild birch has little geographic area, PFS to *Rosaceae* fruits and soybean caused by Bet v 1 homologue sensitization has been recently reported throughout the country.^{10,11} This is suggested to be due to the wide distribution of alder and other Betulaceae species, which release pollen closely related to birch pollen and cause spring allergic rhinitis in Japan.¹² A case series conducted among 11 tertiary medical centers from different areas in Japan has reported that *Rosaceae* fruits, most commonly apple and peach, were the causative foods based on history and skin prick test (SPT) among half of the entire cases of PFS.¹³ Another Japanese study among outpatients of a dermatology department also showed that apple and peach were the most common foods causing PFS, based on the history and positive SPT.¹¹ They also reported that PFS to those two fruits showed a significant association with sensitization to alder pollen. Interestingly, while many patients in this study were sensitized to Japanese cedar pollen, this was not associated with having PFS to previously reported cross-reacting foods such as tomato.¹⁴

While patients with PFS to Bet v1 related food allergens appear to be increasing in Japan, previous reports are limited to clinic-based studies and case reports, with even less data on the prevalence in children. Furthermore, recent data suggesting the continuing rise in the prevalence of seasonal allergic rhinitis in children may be expected to translate to an increase in PFS.¹⁵

In 2015, we conducted a nation-wide school-based questionnaire study to investigate the burden of allergic disease among Japanese children. Using this data, we aimed to estimate the prevalence and risk factors for PFS by investigating the prevalence and characteristics of children with oral symptoms to Bet v 1 related foods.

Methods

Study design

The method of this study has been previously described in detail.¹⁶ In brief, a school-based, cross-sectional sampling of primary and secondary school students was used to recruit a sample of 1000 children in two age groups; primary school students (Years 1–2) and secondary school students (Years 8–9) from each of the 47 prefectures in Japan. Questionnaires were distributed and collected through participating schools by mail and were asked to be completed by the parents for primary school students, and themselves by secondary school students.

Questionnaires and definitions

The questionnaire collected demographic details, lifestyle factors and family and personal history of allergic disease. Children with oral symptoms were defined as those who had a positive response to the question “Does your child (Do you, for students in secondary schools) feel tingling, numbness, itchiness or swelling in the mouth or throat immediately or within 15 min after eating fresh fruit or vegetables?” Children with a positive response to the previous question were then asked to choose the causative food/foods from apple, peach, cherry, soybean (including its products), kiwi and melon, which we selected based on the most common causative foods of PFS in a previous case series conducted in Japan.¹³ Children with oral symptoms to *Rosaceae* fruits were defined as children selecting apple, peach and cherry as the causative food for their symptoms. We used the Japanese version of ISAAC (International Study of Asthma and Allergies in Childhood)

questionnaire to collect the children's history of wheeze, eczema and allergic rhinitis.^{17,18} History of food allergy was assessed by a parent or self-report of allergy to egg, milk, wheat, shrimp, buckwheat and peanut, based on the most common allergens for Japanese children. The definitions of allergic disease are summarized in the [Supplementary Table 1](#).

Parental history of allergic disease was defined as having a history of asthma, eczema, allergic rhinitis (including hay fever) or food allergy.

Geographic difference in pollen sensitization

To investigate the association between the prevalence of oral symptoms to *Rosaceae* plants/soybeans and the geographical difference in alder pollen exposure, we used sensitization rates derived from a database created by combining data from three major test labs operating nationwide in Japan,¹⁹ since nation-wide data on pollen counts were not available. Alder pollen sensitization rates by prefectures were calculated as the proportion of test results with positive alder pollen specific IgE (>0.7 IU/ml) among the tests conducted through pediatric clinics or departments for each prefecture.

Statistical analysis

The prevalence estimate for oral symptoms was calculated as the observed proportion with 95% confidence interval (CI) for each age group. Demographic and clinical characteristics between children with and without oral symptoms to *Rosaceae* fruits and soybean were compared by Pearson's chi square tests for categorical variables and t-test for continuous variables. We used multiple logistic regression to analyze the association of allergic rhinitis and asthma with the prevalence of oral symptoms. Sex and family history were considered a priori as an important risk factor from previously published reports. Other demographic and environmental factors were only retained as confounding variables if they altered the magnitude of the estimated odds ratio for the association between the factor of interest and the prevalence of oral symptoms by more than 10%. The correlation between the prevalence of oral symptoms and the pollen sensitization rates by prefecture was assessed by Spearman's correlation coefficient. All statistical analysis was undertaken using Stata version 15.1 (StataCorp, College Station, TX, USA).

Ethical considerations

The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Health, Labour and Welfare of Japan. The study was approved by the ethics review board of Tokyo Metropolitan Children's Medical Center (ID: H26-123).

An information sheet for the parents explaining the object of the study was attached to the questionnaire and indicated that participation was voluntary. Students returning their questionnaires to schools were considered to have given consent to participation in the survey. The questionnaire was anonymous with only the school name to link their geographic location of residence for analysis.

Results

School and student participation rates are shown in [Figure 1](#). Overall, the student participation rates, calculated as the number of students who participated among the total number of eligible

students in the schools that participated, were 82.9% and 68.6% for primary school students and secondary school students, respectively.

Prevalence and characteristics of children with oral symptoms to *Rosaceae* fruits or soybean

The prevalence of oral symptoms to *Rosaceae* fruits or soybean was 0.99% (95%CI, 0.89–1.09) for primary school students and 2.75% (95%CI, 2.59–2.93) for secondary school students (Table 1). Peach was the most common causative food in both age groups at 0.63% (95%CI, 0.56–0.71) and 1.79% (95%CI, 1.65–1.93), respectively, followed by apple with a prevalence of 0.29% (95%CI, 0.24–0.35) and 1.50% (95%CI, 1.37–1.63), respectively. Among children with oral symptoms to these foods, 79% (323 of 407) reacted to one food in primary school students, while 43% (421 of 972) reacted to multiple foods in secondary school students. The prevalence of oral symptoms in each prefecture is described in Figure 2. The prevalence ranged from 0 to 3.71% with a median of 0.91% for primary school students and ranged from 0.17 to 12.3% with a median of 1.79% for secondary school students. For both age groups, prevalence in the highest quartile was seen in Hokkaido (the northern island of Japan) and in several prefectures in the central and western regions of the main island.

The demographic and clinical characteristics of children with and without oral symptoms to *Rosaceae* fruits or soybean among the total respondents are compared for each age group in Table 2. There was a higher proportion of children with parental history of allergic disease, as well as personal history of food allergy, asthma, allergic rhinitis or eczema in children with oral symptoms compared to those without symptoms for both age groups. Among the children with oral symptoms, 73.0% primary school students

Table 1

Prevalence of oral symptoms to *Rosaceae* fruits or soybean.

	Primary school students (n = 41,264)			Secondary school students (n = 35,302)		
	n	%	95%CI	n	%	95%CI
Causative foods						
Peach	261	0.63	0.56–0.71	631	1.79	1.65–1.93
Apple	119	0.29	0.24–0.35	528	1.50	1.37–1.63
Cherry	107	0.26	0.21–0.31	390	1.10	1.00–1.22
Soybean	26	0.06	0.04–0.09	105	0.30	0.24–0.36
Any of the above	407	0.99	0.89–1.09	972	2.75	2.59–2.93
Number of causative foods [†]						
single	323	0.78	0.70–0.87	551	1.56	1.43–1.70
multiple	84	0.20	0.16–0.25	421	1.19	1.08–1.31

Prevalence was estimated using observed proportions, with 95% confidence intervals (CI) for each age group.

[†] Number of foods among peach, apple, cherry or soybean.

and 82.3% secondary school students had current allergic rhinitis, and most had symptoms in spring.

The association between oral symptoms to *Rosaceae* fruits or soybean and allergic rhinitis and asthma

We further explored the association of allergic rhinitis and asthma to having oral symptoms to *Rosaceae* fruits or soybean in Table 3. Birth weight, mode of delivery, number of siblings, paternal and maternal education, smoker in the household and pet exposure were considered but not included in the final model because they did not change the magnitude of the estimated odds ratio for the association between the factor of interest and the prevalence of oral symptoms. Compared to children without allergic rhinitis, those with spring allergic rhinitis were 5 times more likely to have oral symptoms when the rhinitis symptoms were severe (adjusted OR [aOR] 5.0, 95%CI: 3.4–7.3 and aOR 4.5, 95%CI: 3.6–5.6 for each age group, respectively), and 3 times more likely when the rhinitis symptoms were mild to moderate (aOR 2.6, 95%CI: 2.1–3.3 and aOR 2.9, 95%CI: 2.4–3.5 for each age group, respectively). Current wheeze was similarly associated with the prevalence of oral symptoms, where the risk was the highest among children with severe wheeze compared to those without wheeze (aOR 3.2, 95%CI: 2.2–4.5 and aOR 2.6, 95%CI: 2.0–3.4, for each age group, respectively). The risk of having oral symptoms was approximately five times as high when the child had both current allergic rhinitis and current wheeze (aOR 4.8, 95%CI: 3.5–6.6 and aOR 4.9, 95%CI: 3.8–6.2 for each age group, respectively) compared to those without allergic rhinitis or wheeze.

Although there was evidence of an association between current eczema and oral symptoms for both age groups (aOR 2.3, 95%CI 1.8–2.8 and aOR 2.3, 95%CI 1.9–2.7, respectively), there was no difference in risk between the severity of disease.

Correlation between the prevalence of oral symptoms to *Rosaceae* fruits or soybean and alder pollen sensitization rates by prefecture (Fig. 3)

Data from the external database showed that alder pollen sensitization rates by prefecture ranged from 0% to 29.3%, which is likely to reflect the wide geographical difference in the amount of alder pollen exposure in Japan. There was a strong positive correlation between the prevalence of oral symptoms and alder sensitization rates by prefecture for both primary school students ($r = 0.63$, $p < 0.001$) and secondary school students ($r = 0.76$, $p < 0.001$) as shown in Figure 3.

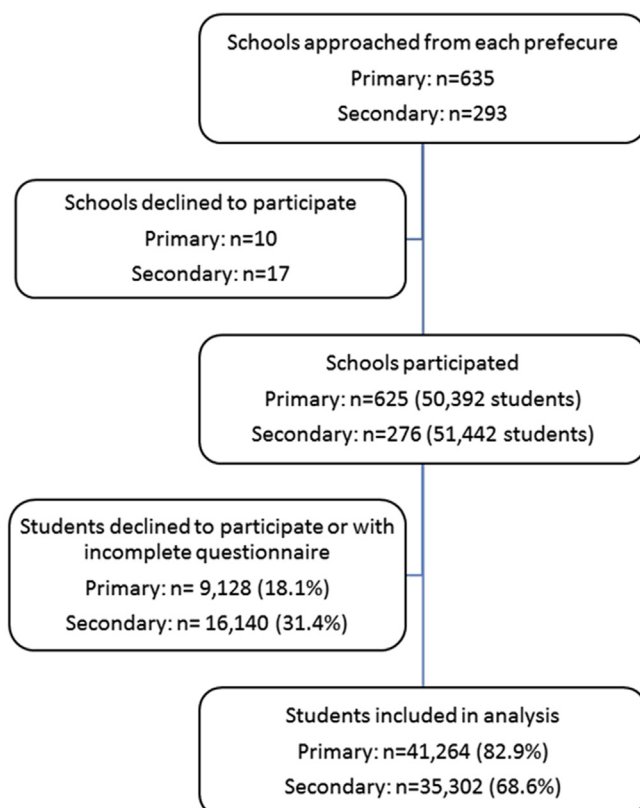


Fig. 1. Overview of the analysis.

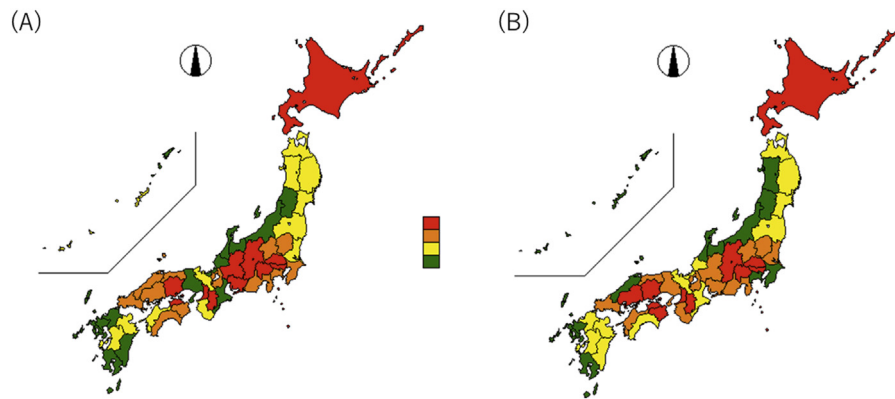


Fig. 2. Prevalence of oral symptoms to *Rosaceae* fruits or soybean among each prefecture on the map of Japan. The prevalence is categorized into quartiles and color-coded for each primary school students (A, lowest quartile in green: 0–0.56%, 2nd quartile in yellow: 0.56–0.91%, 3rd quartile in orange: 0.91–1.28%, highest quartile in red: 1.28–3.71%) and secondary school students (B, lowest quartile in green: 0.17–1.05%, 2nd quartile in yellow: 1.05–1.79%, 3rd quartile in orange: 1.79–3.69%, highest quartile in red: 3.69–12.3%).

Table 2
Demographic and clinical characteristics of children with and without oral symptoms to *Rosaceae* fruits or soybean.

	Primary school students [†]					Secondary school students [‡]				
	Oral symptoms		No oral symptoms		p value	Oral symptoms		No oral symptoms		p value
	N	%	N	%		N	%	N	%	
Total	407/41,264	0.99	10,857/41,264	99.0		972/35,302	2.75	34,330/35,302	97.2	
Sex										
male	197/407	48.4	20,626/40,718	50.7	0.366	406/969	41.9	16,736/34,146	49.0	<0.001
female	210/407	51.6	20,092/40,718	49.3		563/969	58.1	17,410/34,146	51.0	
Age mean ± SD	6.8 ± 0.7		6.7 ± 0.7		0.215	13.7 ± 0.6		13.7 ± 0.7		0.157
Parent's final education university degree or higher										
Father	149/382	38.5	13,705/38,963	35.2	0.173	304/861	35.3	8966/29,826	30.1	0.001
Mother	66/394	16.8	7256/39,735	18.3	0.440	130/879	14.8	3994/30,905	12.9	0.104
Parental history of allergic disease										
Father	281/377	74.5	20,205/37,704	53.6	<0.001	468/831	56.3	12,255/28,817	42.5	<0.001
Mother	289/387	74.7	22,074/39,168	56.4	<0.001	543/868	62.6	14,373/30,076	47.8	<0.001
Food allergy [‡]										
Food allergy ever	159/377	42.2	4389/40,244	10.9	<0.001	243/854	28.5	2732/33,596	8.1	<0.001
Current food allergy	99/354	28.0	1403/39,042	3.6	<0.001	146/823	17.7	1045/32,971	3.2	<0.001
Asthma										
Asthma ever	134/403	33.3	6851/40,654	16.9	<0.001	271/967	28.0	6423/33,981	18.9	<0.001
Current wheeze	90/404	22.3	4024/40,476	9.9	<0.001	154/967	15.9	2672/33,966	7.9	<0.001
Allergic rhinitis										
Hay fever ever	229/403	56.8	9232/40,578	22.8	<0.001	790/965	81.9	15,635/34,030	45.9	<0.001
Current allergic rhinitis	297/407	73.0	19,250/40,640	47.4	<0.001	791/961	82.3	20,525/33,957	60.4	<0.001
Spring allergic rhinitis [§]	272/400	68.0	9232/40,578	22.8	<0.001	734/951	77.2	16,643/33,155	50.2	<0.001
Current allergic rhino-conjunctivitis	179/407	44.3	7436/40,521	18.4	<0.001	527/953	55.3	8690/33,766	25.7	<0.001
Eczema										
Eczema ever	333/206	82.0	25,772/40,680	63.4	<0.001	554/955	58.0	14,235/33,845	42.1	<0.001
Current eczema	119/388	30.7	5805/39,409	14.7	<0.001	195/934	20.9	3134/33,135	9.5	<0.001

[†] Numbers may not add up to total because of missing data.

[‡] History of food allergy was assessed for egg, milk, wheat, shrimp, buckwheat and peanut.

[§] Spring allergic rhinitis was defined as children having rhinitis symptoms in March, April or May in the past year.

Discussion

We have demonstrated that oral symptoms to *Rosaceae* fruits/soybean, which is suggestive of PFS was reported by 1–3% of Japanese children using a nation-wide study. This is the first population-based study to give an estimate of the prevalence and its characteristics of PFS in Japanese children.

The prevalence showed a wide geographical variation with a consistent pattern between primary and secondary school students. In addition to the northern island, Hokkaido, prefectures with higher prevalence were found in a wider area in the central and western regions of the main island. Since wild birch only grows in Hokkaido and very few prefectures in central Japan, this distribution supports the hypothesized role of alder and other

Betulaceae species in the development of oral symptoms among areas of Japan without birch.

The major limitation of this study is that it was a questionnaire-based survey using solely self-reported oral symptoms to the specific foods shortly after ingestion to identify children with possible PFS. Since objective information such as sensitization data or results from oral challenge tests to these foods were not available, it is possible that we have included children with oral symptoms due to non-allergic causes or due to primary sensitization to these foods. However, previous studies have shown that a positive clinical history has a high sensitivity and specificity in detecting PFS.^{7,20,21} A group in UK has reported that clinical history of oral symptoms caused by specific foods occurring within 15 min of ingestion assessed by a PFS diagnostic questionnaire successfully identified

Table 3The association of allergic rhinitis and asthma to having oral symptoms to *Rosaceae* fruits or soybean[†].

	Primary school students				Secondary school students			
	% [‡]	n/N	aOR [§] , 95%CI	p value	% [‡]	n/N	aOR [§] , 95%CI	p value
Current allergic rhinitis								
No allergic rhinitis	0.5	110/21,500	1		1.3	170/13,602	1	
Non-spring allergic rhinitis	0.9	18/2091	1.5, 0.9–2.6	0.103	1.5	47/3127	1.2, 0.8–1.7	0.386
Mild to moderate spring rhinitis	1.5	235/15,419	2.6, 2.1–3.3	<0.001	3.8	530/13,919	2.9, 2.4–3.5	<0.001
Severe spring rhinitis	2.9	37/1293	5.0, 3.4–7.3	<0.001	5.9	201/3394	4.5, 3.6–5.6	<0.001
Current wheeze								
None	0.9	317/36,924	1		2.5	816/32,268	1	
Mild-moderate	1.9	56/2959	1.9, 1.4–2.6	<0.001	4.6	82/1770	1.8, 1.4–2.3	<0.001
Severe wheeze	2.9	34/1155	3.2, 2.2–4.5	<0.001	6.8	72/1056	2.6, 2.0–3.4	<0.001
Comorbid current allergic rhinitis and current wheeze								
No allergic rhinitis or wheeze	0.5	95/20,091	1		1.2	158/12,983	1	
Wheeze only	1.2	15/1283	2.1, 1.2–3.7	0.001	2.3	12/532	2.0, 1.1–3.7	0.030
Allergic rhinitis only	1.3	222/16,634	2.5, 1.9–3.2	<0.001	3.4	648/18,941	2.7, 2.3–3.3	<0.001
Allergic rhinitis and wheeze	2.6	75/2821	4.8, 3.5–6.6	<0.001	6.2	141/2263	4.9, 3.8–6.2	<0.001

[†] Spring allergic rhinitis was defined as children who had rhinitis symptoms in March, April or May in the past year. Non-spring allergic rhinitis was defined as children who had rhinitis symptoms only in other months than March, April or May.

[‡] Proportion of children with oral symptoms to *Rosaceae* fruits or soybean in each category.

[§] aOR (adjusted OR), adjusted for sex and family history of allergy.

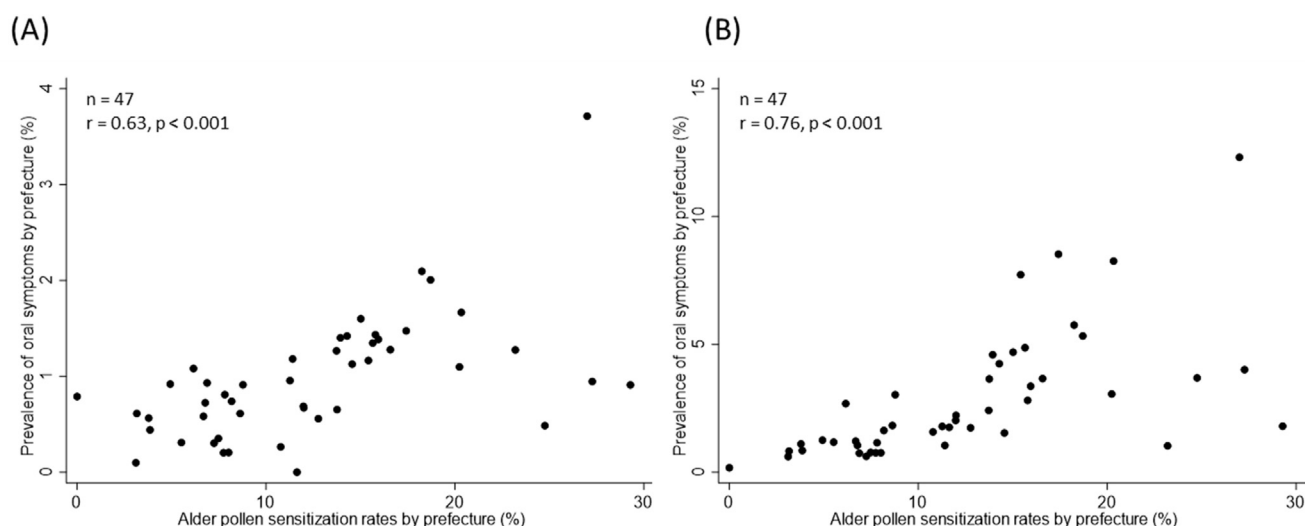


Fig. 3. Correlation between prevalence of oral symptoms to *Rosaceae* fruits or soybean and alder pollen sensitization rates by prefecture in primary school students (A) and secondary school students (B). Alder pollen sensitization rates were derived using external data from three major test labs.¹⁹ It was calculated as the proportion of tests with positive alder specific IgE (>0.7IU/ml) among the tests conducted through pediatric clinics and departments for each of the 47 prefectures in Japan. Spearman's correlation coefficient was used for statistical testing.

95% of cases with PFS who were formally diagnosed through skin prick testing and oral food challenges.^{7,9} Nonetheless, we have classified the children captured by our questionnaire as those with oral symptoms to *Rosaceae* fruits/soybean, and not as those with PFS. Another limitation of our study due to the lack of sensitization data is that we were not able to show the association between oral symptoms and alder pollinosis at the individual level. It is possible that children with spring allergic rhinitis include not only those with pollinosis to alder, which releases its pollen mainly around March and April, but also those with allergy to Japanese cedar pollen (mainly released between February and May), cypress pollen (mainly in March and April) and orchard grass pollen (from April to July).²² The sensitization rates of these pollens for each prefecture are shown in [Supplementary Table 2](#). Additionally, it is possible that the correlation between oral symptoms and sensitization to crude alder pollen is confounded by the sensitization to grass pollens, which is known as a major source of sensitization to the plant

panallergen profilin. Profilin-sensitized children may have oral symptoms due to the cross-reactivity between profilins in these foods and in grass pollen, and not due to the sensitization to Bet v 1, but nevertheless test positive to crude alder pollen IgE since the extract also contains profilin. However, there was only a weak correlation between the prevalence of oral symptoms and the sensitization rates to orchard grass ([Supplementary Fig. 1](#)), which did not remain after adjusting for alder pollen sensitization rates. There was also no correlation between oral symptoms and the sensitization rates to Japanese cedar pollen or cypress pollen when adjusted for alder pollen sensitization rates (data not shown). Notwithstanding the limitation of this ecological analysis, we consider that this result supports the role of underlying sensitization to Bet v 1 in the self-reported oral symptoms, as well as the validity of our questionnaire.

As expected, having oral symptoms was significantly associated with family history and personal history of allergic disease,

supporting the role of atopic predisposition in this disease. It was more common among secondary school students compared to primary school students. This may partially be due to the difference in recognition of symptoms, but it is in agreement with the result from the UK study reporting the onset of PFS being most likely in late childhood.⁹ The female predominance shown in secondary school students is in line with several previous reports.^{4,9} Although hormonal influences may have a role in this possible gender difference as previously suggested for other allergic diseases,²³ over-reporting by females is also possible.

Additionally, we have shown that oral symptoms were more likely to be found in children with severe rhinitis symptoms compared to those with no or mild to moderate symptoms. Birch pollen specific IgE levels and Bet v 1 specific IgE levels are reported to be significantly higher among patients with PFS compared to those without PFS among birch pollen allergic patients.³ Since there are some studies showing that levels of specific IgE to pollen are association with the severity of seasonal allergic rhinitis,²⁴ the positive association we found between rhinitis severity and oral symptoms may reflect the level of sensitization to alder pollen. However, previous data on the relationship between PFS and the severity of allergic rhinitis symptoms is limited. In an Italian study of 4–18 years old children with seasonal allergic rhinitis among 16 pediatric outpatient clinics in multiple cities, 24% reported PFS with no difference in the severity of rhinitis compared to those without PFS.⁴ The inconsistency with our results may be due to the difference in the study design, population-based vs clinic based, or the difference in the underlying pattern of sensitization. The association between oral symptoms and wheeze and its severity showed a similar pattern even after adjusting for comorbid allergic rhinitis in our study (data not shown), suggesting that wheeze was independently associated with having oral symptoms. Whether this is also possibly a result of higher level of sensitization as hypothesized in the association with severe rhinitis, or whether there is another mechanism is not yet clear.

In conclusion, we found that possible PFS to *Rosaceae* fruit or soybean was relatively common among Japanese children. Our results suggest that children with severe spring rhinitis, severe wheeze or those who have both allergic rhinitis and wheeze may have a higher risk of having oral symptoms to these foods. It is important that we further investigate the risk factors for PFS among children to identify the group who would benefit from patient education or possibly treatment in the future.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.03.011>.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MS, EM, KY, YA, HO and AA designed the study. MS, EM, KY and AA coordinated the study and collected data. YF provided the external nationwide pollen

sensitization data and assisted with the analysis. MS conducted the data analysis and wrote the manuscript. All authors contributed to the interpretation of data and revision of the manuscript.

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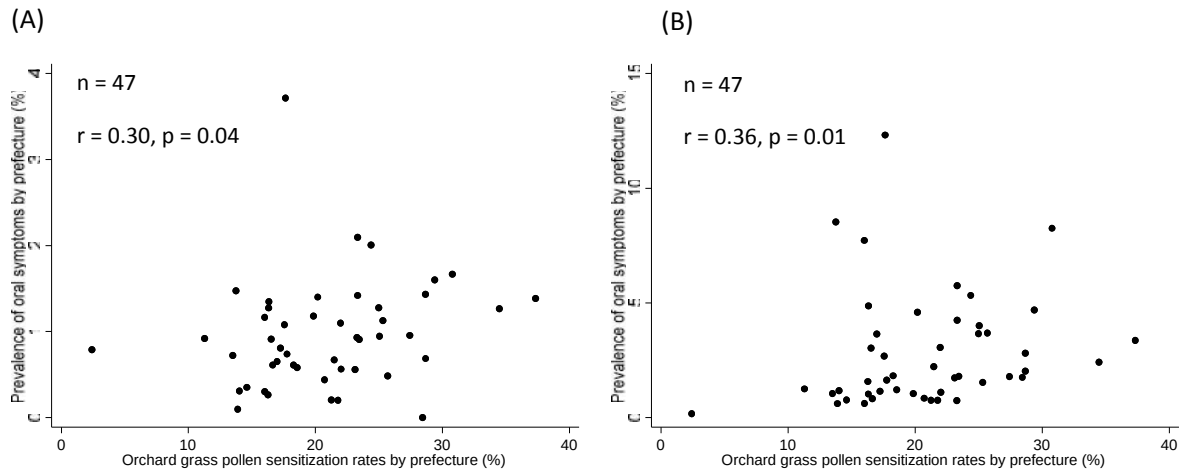
Supplementary Table 1. Summary of definitions

Allergic disease	Definition
Oral symptoms to <i>Rosaceae</i> fruits or soybean	Positive response to “Does your child /Do you feel tingling, numbness, itchiness or swelling in the mouth or throat immediately or within 15 minutes after eating fresh fruit or vegetables?” and selecting apple, peach, cherry or soybean (including soybean products) as the causative food.
Asthma ever	Positive answer to the question ‘Has your child/ Have you ever had asthma?’
Current wheeze	Positive response to the questions, ‘Has your child / Have you had wheezing or whistling in the chest in the last 12 months?’ Current wheeze was further categorized as severe wheeze when having positive response to one or more of the following, wheezing severe enough to limit the child’s speech to only one or two words at a time between breaths, more than 12 attacks in the past 12 months, or sleep disturbed due to wheezing more than one night per week. Current wheeze was categorized as mild to moderate wheeze when none of the questions above had a positive response.
Hay fever ever	Positive response to the question ‘Has your child/ Have you ever had hay fever?’
Current allergic rhinitis	Positive response to the question, ‘In the past 12 months, has your child/ have you had a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu?’ The severity of current rhinitis based on the interference with daily activities was determined by the question, ‘In the past 12 months, how much did this nose problem interfere with your daily activities?’, where the response of ‘not at all’, ‘a little’, ‘a moderate amount’ was classified as mild to moderate severity and the response of ‘a lot’ as severe.
Spring allergic rhinitis	Selecting March, April or May to the question, ‘In which or the past 12 months did this nose problem occur?’ among children with current rhinitis.
Current allergic rhino-conjunctivitis	Positive response to ‘In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?’ among children with current rhinitis.
Eczema ever	Positive answer to the question ‘Has your child/ Have you ever had eczema?’
Current eczema	Positive response to the following questions, ‘Has your child/ Have you ever had an itchy rash which was coming and going for at least 6 months?’, ‘Has your child / Have you had this itchy rash at any time in the past 12 months?’ and ‘Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?’
Food allergy ever	Positive response to ‘Has your child/ have you ever had food allergy?’ and selecting one or more of the following allergens; egg, milk, wheat, shrimp, buck wheat or peanut.
Current food allergy	Positive response to ‘Is your child/Are you still allergic to the food?’ among the children with food allergy ever to egg, milk, wheat, shrimp, buck wheat or peanut.

Supplementary Table 2. Pollen sensitization rates of alder, Japanese cedar, cypress and orchard grass
by each prefecture in Japan†

	Prefecture	alder (%)	Japanese cedar (%)	cypress (%)	orchard grass (%)
1	Hokkaido	17.4	5.0	4.5	13.8
2	Aomori	3.8	25.2	8.5	22.0
3	Iwate	6.7	36.5	11.8	18.6
4	Miyagi	8.6	41.6	18.0	18.3
5	Akita	6.8	20.5	6.4	13.5
6	Yamagata	8.0	28.1	9.5	21.3
7	Fukushima	8.2	46.9	18.6	17.8
8	Ibaraki	12.0	51.0	32.2	21.5
9	Tochigi	20.2	53.3	34.3	22.0
10	Gunma	16.6	47.9	30.0	25.0
11	Saitama	18.7	48.2	31.5	24.4
12	Chiba	11.4	50.5	28.7	19.9
13	Tokyo	15.7	49.6	31.4	16.3
14	Kanagawa	23.2	46.7	28.7	16.3
15	Niigata	7.5	31.0	7.0	14.6
16	Toyama	7.8	28.5	15.1	21.8
17	Ishikawa	3.9	26.2	9.5	20.7
18	Fukui	12.8	46.5	26.8	23.1
19	Yamanashi	27.0	51.1	43.9	17.6
20	Nagano	20.3	46.8	33.1	30.8
21	Gifu	16.0	44.5	37.2	37.3
22	Shizuoka	8.8	40.7	31.3	16.5
23	Aichi	15.8	40.3	31.3	28.7
24	Mie	11.6	57.3	39.1	28.4
25	Shiga	11.3	39.1	31.1	27.4
26	Kyoto	14.6	43.6	33.7	25.3
27	Osaka	14.3	33.3	26.0	23.3
28	Hyogo	24.8	31.6	28.3	25.7
29	Nara	15.0	39.1	32.9	29.4
30	Wakayama	13.8	31.7	19.5	17.0
31	Tottori	13.7	39.6	23.9	34.5
32	Shimane	6.9	27.3	21.9	23.3
33	Okayama	18.3	36.9	29.9	23.3
34	Hiroshima	15.4	26.0	19.8	16.0
35	Yamaguchi	6.2	33.9	21.4	17.6
36	Tokushima	27.3	34.3	28.1	25.0
37	Kagawa	13.9	22.8	16.2	20.2
38	Ehime	29.3	36.0	29.1	23.4
39	Kochi	4.9	37.3	22.7	11.3
40	Fukuoka	5.5	30.1	18.9	14.0
41	Saga	7.3	26.9	21.0	16.0
42	Nagasaki	3.2	30.2	20.0	16.6
43	Kumamoto	12.0	31.3	24.6	28.7
44	Oita	7.8	35.2	23.1	17.2
45	Miyazaki	10.8	28.0	14.4	16.3
46	Kagoshima	3.1	21.7	14.0	13.9
47	Okinawa	0.0	5.3	1.4	2.4

† Sensitization rates were derived using external data from three major test labs.¹ It was calculated as the proportion of tests with positive specific IgE (>0.7 IU/ml) among the tests conducted for each pollen allergens through pediatric clinics and departments for each of the 47 prefectures in Japan.



Supplementary Fig. 1. Correlation between prevalence of oral symptoms to *Rosaceae* fruits or soybean and orchard grass pollen sensitization rates by prefecture in primary school students (A) and secondary school students (B).

Orchard pollen sensitization rates were derived using external data from three major test labs.¹ It was calculated as the proportion of tests with positive orchard specific IgE (>0.7 IU/ml) among the tests conducted through pediatric clinics and departments for each of the 47 prefectures in Japan. Spearman's correlation coefficient was used for statistical testing.

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