

## Original Article



# Pollen-Food Allergy Syndrome in Korean Pollinosis Patients: A Nationwide Survey

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## ABSTRACT

**Purpose:** Pollen-food allergy syndrome (PFAS) is an immunoglobulin E (IgE)-mediated allergy in pollinosis patients caused by raw fruits and vegetables and is the most common food allergy in adults. However, there has been no nationwide study on PFAS in Korea. In this study, we investigated the prevalence and clinical characteristics of PFAS in Korea.

**Methods:** Twenty-two investigators participated in this study, in which patients with allergic rhinoconjunctivitis and/or bronchial asthma with pollen allergy were enrolled. The

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questionnaires included demographic characteristics, a list of fruits and vegetables, and clinical manifestations of food allergy. Pollen allergy was diagnosed by skin prick test and/or measurement of the serum level of specific IgE.

**Results:** A total of 648 pollinosis patients were enrolled. The prevalence of PFAS was 41.7% (n = 270). PFAS patients exhibited cutaneous (43.0%), respiratory (20.0%), cardiovascular (3.7%) or neurologic symptoms (4.8%) in addition to oropharyngeal symptoms. Anaphylaxis was noted in 8.9% of the PFAS patients. Seventy types of foods were linked to PFAS; *e.g.*, peach (48.5%), apple (46.7%), kiwi (30.4%), peanut (17.4%), plum (16.3%), chestnut (14.8%), pineapple (13.7%), walnut (14.1%), Korean melon (12.6%), tomato (11.9%), melon (11.5%) and apricot (10.7%). Korean foods such as taro/taro stem (8.9%), ginseong (8.2%), perilla leaf (4.4%), bellflower root (4.4%), crown daisy (3.0%), deodeok (3.3%), kudzu root (3.0%) and lotus root (2.6%) were also linked to PFAS.

**Conclusions:** This was the first nationwide study of PFAS in Korea. The prevalence of PFAS was 41.7%, and 8.9% of the PFAS patients had anaphylaxis. These results will provide clinically useful information to physicians.

**Keywords:** Pollen-food allergy syndrome; pollen; food allergy

## INTRODUCTION

Pollen-food allergy syndrome (PFAS) is a class 2 food allergy caused by respiratory exposure to pollen; in contrast, class 1 food allergies are sensitized by the gastrointestinal tract. The pathogenesis of PFAS is related to cross-allergenicity between pollen and foods such as fruits and vegetables.<sup>1,2</sup> The term oral allergy syndrome (OAS) is traditionally used for PFAS, but can be confusing. OAS indicates immunoglobulin E (IgE)-mediated immediate allergy symptoms restricted to the oral mucosa, which is the most common clinical presentation of PFAS.<sup>2</sup> Since OAS in pollinosis patients was first reported in 1942 as labile antigen in fresh fruit extracts,<sup>3</sup> many subsequent studies reported that OAS can involve systemic symptoms such as urticaria, nausea, vomiting and anaphylaxis.<sup>4-6</sup>

In 1982, the first investigation of PFAS in European pollinosis patients reported a prevalence of more than 70%. Indeed, 19% of pollinosis patients sensitized to mugwort or grass pollen have a food hypersensitivity.<sup>4</sup> The prevalence of PFAS in pollinosis patients is around 40%–50% in Europe<sup>5,7</sup> and 20% in the Mediterranean region (a birch- and ragweed-free area).<sup>8</sup> The prevalence of PFAS in pediatric pollinosis patients is around 9%–12%; *e.g.*, 9.6%–12.2% in Mexico and 12.1% in Australia.<sup>9,11</sup> In Japan, 7%–17% of OAS occurs in cedar pollinosis patients.<sup>12,13</sup> In another study in Japan, the overall prevalence of OAS was 4.1% in the pollen-sensitized population, comprising 4% in Japanese cedar pollen, 11.5% in alder, 5.5% in orchard grass, 7.4% in ragweed and 6.4% in mugwort, where the most common causes were apple, peach and melon.<sup>14</sup> Thus, few studies of the epidemiology and clinical characteristics of PFAS have involved children or been performed in Asian countries.

The sole previous study of PFAS in Korea reported a PFAS prevalence of 34.6% in pollen-sensitized patients in a single general hospital (48% in tree pollen- and 13% in grass or weed pollen-sensitized patients), and apple was the most common causative food.<sup>15</sup> However, this was a small retrospective study involving only 81 subjects. Therefore, we investigated the prevalence and clinical features of PFAS in Korean pollinosis patients by means of a nationwide survey.

## MATERIALS AND METHODS

### Study design

This was a nationwide cross-sectional study in 20 institutes (18 university hospitals and 2 allergy clinics). The protocol was reviewed and approved by the Institutional Review Board of each institute (Hallym University Dongtan Sacred Heart Hospital, HDT-2016-04-155-003, *etc.*). Written informed consent was obtained from each patient or their parents.

### Patients

Pollinosis patients were enrolled from March to December 2016. The inclusion criteria were as follows: 1) diagnosis with one or more of allergic rhinitis (AR), allergic conjunctivitis (AC) and/or bronchial asthma (BA); 2) sensitization to the pollen of 1 or more trees, grasses and/or weeds; and 3) aggravated symptoms of rhinitis, conjunctivitis and/or asthma when exposed to sensitized pollens. Patients who fulfilled at least one of the following criteria were regarded as being sensitized to pollen: 1) allergen wheal size greater or equal to that of histamine (A/H ratio  $\geq 3+$ ) or mean allergen wheal diameter of at least 3 mm by skin prick test (SPT);<sup>16,17</sup> 2) a multiple allergen simultaneous test (MAST) result of at least 2+; and 3) a serum specific IgE level of at least 0.35 kU/L measured by the ImmunoCAP® system (ThermoFisher Scientific, Uppsala, Sweden). The pollens investigated comprised tree pollens (birch, alder, hazel, beech, oak, willow, poplar, pine and tree mix), grass pollens (Bermuda, meadow, orchard, rye, timothy and grass mix) and weed pollens (mugwort, ragweed and *Hop Japanese*).

### Clinical data collection

Clinical data were collected by questionnaire and chart review, and included demographic characteristics, underlying allergic diseases, and results of allergic tests. The demographic data included sex, birth date, birthplace, present residence area, height, body weight, family history of allergic diseases, smoking status (current, former, or never-smoker), and history of second-hand smoking. AR severity and symptom duration were classified using the Allergic Rhinitis and its Impact on Asthma (ARIA) system.<sup>18</sup> Briefly, severity was classified as mild or moderate-severe, and symptom duration as intermittent or persistent. Moderate-severe rhinitis symptoms were defined as 1 or more bothersome symptoms such as sleep disturbance, impairment of daily activity, impairment of school or work, and troublesome symptoms. Persistent rhinitis was defined as symptoms on more than 4 days per week for at least 4 consecutive weeks. The results of allergy tests for house dust mite, cat, dog and fungus allergens were also obtained.

### Questionnaires about PFAS

All subjects completed questionnaires about PFAS. The questionnaires included the following questions: 1) Have you experienced any symptoms after ingesting any of the foods listed below? and 2) If any, which symptoms have you had? The food list contained common fruits and vegetables in South Korea — apple, pear, peach, apricot, plum, cherry, watermelon, melon, Korean melon, banana, kiwi, orange, mandarin, pineapple, strawberry, mango, avocado, grape, carrot, potato, sweet potato, celery, crown daisy, perilla leaf, lettuce, kale, chicory, taro/taro stem, ginseng, deodeok (*Codonopsis lanceolata*), bellflower root, kudzu, lotus root, Chinese yam, eggplant, zucchini, cucumber, tomato, jujube, chestnut, peanut, walnut, pine nut and soy. The patients were also asked to record any other fruits or vegetables that caused allergy symptoms. The cooking status of the fruits and vegetables (raw and cooked) was also checked.

Symptoms of food allergy were evaluated according to the affected system — oral allergy symptoms (tingling/itching sense or edema of the lips, oral cavity, and/or throat), dermatologic symptoms (itching, urticaria or angioedema), respiratory symptoms (rhinorrhea, cough, dyspnea, wheezing, cyanosis or hypoxia), cardiovascular symptoms (chest pain, hypotension, pale, sweating or cardiac arrest), gastrointestinal symptoms (nausea or vomiting, diarrhea or abdominal pain), neurologic and systemic symptoms (dizziness, unconsciousness, anxiety, change of sense or death) and anaphylaxis.

### Statistical analysis

Statistical analyses were performed using R version 3.4.0 (R Foundation, Vienna, Austria). The Wilcoxon rank-sum test and  $\chi^2$  test were used to compare continuous and categorical clinical variables, respectively, according to PFAS. The CORRPLOT package was used to conduct Yules' Q correlation analysis to identify associations among ordinal variables, and *P* values were calculated by the  $\chi^2$  test. The variables were ordered by the complete-linkage hierarchical clustering method.

## RESULTS

### Clinical characteristics

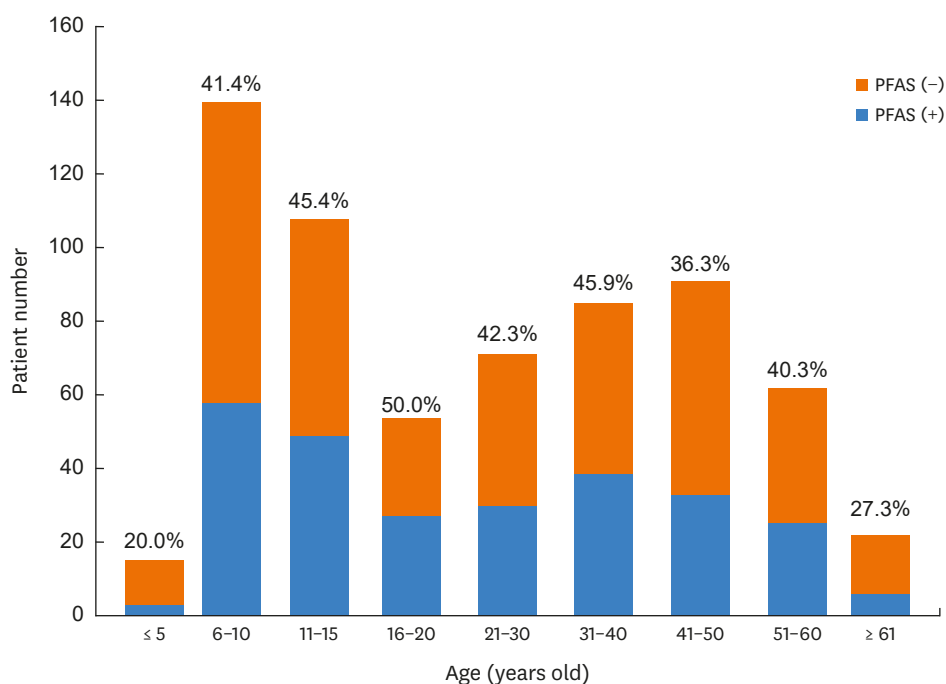
A total of 648 pollinosis patients were enrolled. Four hundred four patients (62.3%) were males, and 300 (42.7%) were less than or equal to 18 years of age. All of the patients had AR (90.1%), AC (45.7%) and/or BA (39.2%), the symptoms of which showed seasonal aggravation; 65.6% in spring, 28.7% in summer, 49.2% in autumn, 32.4% in winter and 17.3% perennially. Of the patients, 68.8% had a family history of allergic diseases.

### Prevalence and clinical characteristics of PFAS patients

Of the 648 pollinosis patients, 270 (41.7%) had PFAS. The prevalence of PFAS did not differ significantly according to age (range, 36.3%–50%), except in those  $\leq 5$  (20%) and  $> 60$  (27.3%) years of age (**Fig. 1**). The prevalence of PFAS in subjects  $\leq 18$  and  $> 18$  years of age was 42.7% (128/300) and 40.8% (142/348), respectively. The prevalence of PFAS differed significantly according to current residence area ( $P < 0.001$ ), and birthplace ( $P = 0.012$ ), and was highest in Gyeonggi, Seoul and Jeolla Provinces (**Supplementary Fig. S1**). The prevalence of PFAS was not different according to birth month ( $P > 0.05$ ).

The clinical characteristics of the patients with PFAS are listed in **Table 1**. Pollinosis patients with PFAS showed higher proportions of female, allergic diseases (such as AR, AC, atopic dermatitis, drug allergy and food allergy), and family history of allergic diseases than those without PFAS. Moderate to severe AR was more prevalent in patients with than in those without PFAS (57.5% vs. 48.4%,  $P = 0.028$ ), while there was no significant difference in the AR symptom duration according to PFAS ( $P > 0.05$ ).

Patients with PFAS had a significantly higher rate of sensitization to alder, birch, beech, hazel, oak, mugwort and cat dander than those without ( $P < 0.01$ , **Fig. 2**). The patients were classified according to the type of pollen to which they were sensitized: only tree pollens (T), only grass pollens (G), only weed pollens (W), tree + grass pollens (TG), tree + weed pollens (TW), grass + weed pollens (GW), or tree, grass, + weed pollens (TGW). Among the 648 pollinosis patients, 174 (26.9%) were classified as T, 36 (5.6%) as G, 52 (8.0%) as W, 51 (7.9%) as TG, 136 (21.0%) as TW, 28 (4.3%) as GW and 171 (26.4%) as TGW. The most frequent



**Fig. 1.** Prevalence of PFAS in various age groups. The prevalence of PFAS did not differ according to age, with the exception of patients less than 5 or more than 60 years of age. PFAS, pollen-food allergy syndrome.

patterns were T, TGW and TW. The prevalence of PFAS was 39.7%, 25%, 21.2%, 33.3%, 55.1%, 28.6% and 47.4% in patients classified as T, G, W, TG, TW, GW and TGW, respectively. Approximately half of the patients classified as TW or TGW had PFAS.

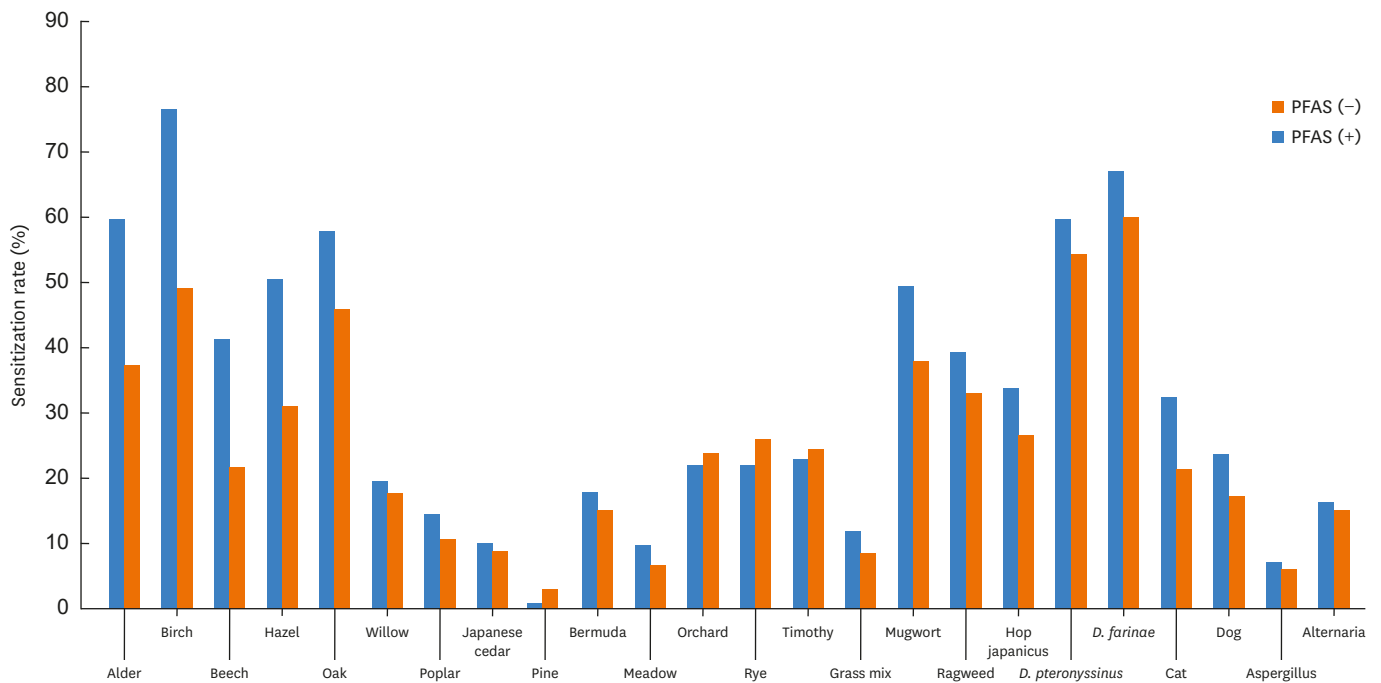
In a subanalysis according to the strength of sensitization to birch, oak, mugwort, ragweed and *Hop Japanese*, the prevalence of PFAS increased significantly with increasing strength of sensitization to birch, oak and mugwort ( $P < 0.05$ ; **Fig. 3**).

**Table 1.** Clinical characteristics of pollinosis patients according to PFAS

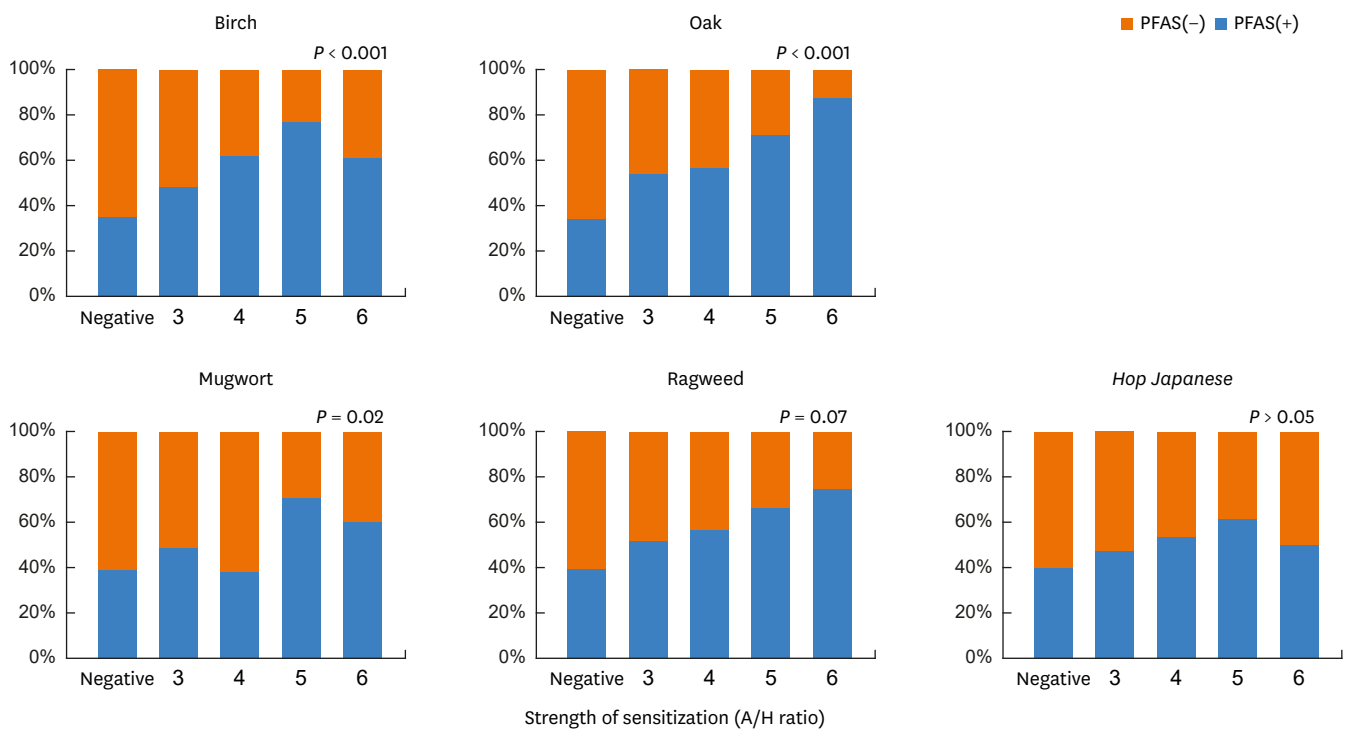
Variables	PFAS (n = 270)	No PFAS (n = 378)	P value
Age	26.1 ± 16.9	27.2 ± 18.4	0.672
Sex (male)	146 (54.1)	258 (68.3)	< 0.001
Allergic diseases			
BA	117 (43.3)	137 (36.2)	0.082
AR	259 (95.9)	325 (86.0)	< 0.001
AC	150 (55.6)	146 (38.6)	< 0.001
Atopic dermatitis	80 (29.6)	67 (17.7)	< 0.001
Chronic urticaria	18 (6.7)	23 (6.1)	0.892
Drug allergy	28 (10.4)	18 (4.8)	0.010
Food allergy	209 (76.7)	53 (14.0)	< 0.001
Family history of allergic disease	201 (74.4)	245 (64.8)	0.012
Severity of AR			0.028
Mild	113/266 (42.5)	192/372 (51.6)	
Moderate/severe	153/266 (57.5)	180/372 (48.4)	
Duration of AR			0.698
Intermittent	118/266 (44.4)	172/372 (46.2)	
Persistent	148/266 (55.6)	200/372 (53.8)	

Data are means ± standard deviation or number (%).

PFAS, pollen-food allergy syndrome; BA, bronchial asthma; AR, allergic rhinitis; AC, allergic conjunctivitis.



**Fig. 2.** Sensitization rate to inhalant allergens according to PFAS. Patients with PFAS had a higher rate of sensitization to alder, birch, beech, hazel, oak, mugwort and cat dander than those without. PFAS, pollen-food allergy syndrome.



**Fig. 3.** Prevalence of PFAS according to strength of sensitization in each pollen. The prevalence of PFAS increased with increasing strength of sensitization. X-axis, strength of sensitization (A/H ratio); Y-axis, prevalence of PFAS (%). PFAS, pollen-food allergy syndrome.

### Clinical manifestations of PFAS

All of the patients had oropharyngeal symptoms, and some had other clinical manifestations of PFAS (**Table 2**). Cutaneous manifestations such as pruritus, urticaria and angioedema were most frequent (43.0%), followed by respiratory (20.0%), gastrointestinal (10.7%), neurologic (4.8%) and cardiovascular (3.7%) symptoms. Interestingly, 8.9% of the PFAS patients experienced anaphylaxis.

### Causative foods

The causative foods of PFAS are shown in **Table 3**. Peach (48.5%) was the food most frequently related to PFAS, followed by apple (46.7%), kiwi (30.4%), peanut (17.4%), plum (16.3%), chestnut (14.8%), walnut (14.1%), pineapple (13.7%), Korean melon (12.6%), tomato (11.9%), melon (11.5%) and apricot (10.7%). The following Korean foods were related to PFAS: taro/taro stems (8.9%), jujube (8.9%), ginseong (8.2%), Chinese yam (7.0%), perilla leaf (4.4%), bellflower root (4.4%), deodeok (*Codonopsis lanceolate*, 3.3%), crown daisy (3.0%), kudzu (3.0%) and lotus root (2.6%).

**Table 2.** Clinical manifestations of PFAS

Clinical manifestations	No. (%)
Cutaneous manifestations	116 (43.0)
Pruritus	79 (68.1)
Urticaria	59 (50.9)
Angioedema	21 (18.1)
Respiratory manifestations	54 (20.0)
Rhinorrhoea	12 (22.2)
Cough	23 (42.6)
Dyspnea	27 (50.0)
Wheezing	5 (9.3)
Cyanosis	2 (3.7)
Gastrointestinal manifestations	29 (10.7)
Nausea/vomiting	20 (69.0)
Diarrhea	8 (27.6)
Abdominal pain	9 (31.0)
Cardiovascular manifestations	10 (3.7)
Chest pain	2 (20.0)
Hypotension	6 (60.0)
Pallor	1 (10.0)
Sweating	5 (50.0)
Neurologic manifestations	13 (4.8)
Dizziness	5 (38.5)
Loss of consciousness	4 (30.8)
Anxiety	3 (23.1)
Paresthesia	4 (30.8)
Anaphylaxis	24 (8.9)

PFAS, pollen-food allergy syndrome.

**Table 3.** Causative foods of PFAS

Foods	No. (%)
Peach	131 (48.5)
Apple	126 (46.7)
Kiwi	82 (30.4)
Peanut	47 (17.4)
Plum	44 (16.3)
Chestnut	40 (14.8)
Walnut	38 (14.1)
Pineapple	37 (13.7)

(continued to the next page)



**Table 3.** (Continued) Causative foods of PFAS

Foods	No. (%)
Korean melon	34 (12.6)
Tomato	32 (11.9)
Melon	31 (11.5)
Apricot	29 (10.7)
Watermelon	26 (9.6)
Cherry	24 (8.9)
Taro/taro stem	24 (8.9)
Jujube	24 (8.9)
Pear	22 (8.2)
Ginseong	22 (8.2)
Pine nut	22 (8.2)
Soy	20 (7.4)
Chinese yam	19 (7.0)
Cucumber	19 (7.0)
Carrot	17 (6.3)
Banana	15 (5.6)
Mango	15 (5.6)
Grapes	14 (5.2)
Perilla leaf	12 (4.4)
Bellflower root	12 (4.4)
Strawberry	11 (4.1)
Potato	10 (3.7)
Celery	9 (3.3)
Deodeok ( <i>Codonopsis lanceolata</i> )	9 (3.3)
Crown daisy	8 (3.0)
Kudzu	8 (3.0)
Lotus root	7 (2.6)
Eggplant	7 (2.6)
Kale	6 (2.2)
Orange	5 (1.9)
Mandarin	5 (1.9)
Zucchini	5 (1.9)
Sweet potato	4 (1.5)
Lettuce	3 (1.1)
Chicory	3 (1.1)
Persimmon	3 (1.1)
Chili	3 (1.1)
Wheat	3 (1.1)
Almond	3 (1.1)
Yacon	3 (1.1)
Avocado	2 (0.7)
Mung bean	2 (0.7)
Perilla	2 (0.7)
Galic	2 (0.7)
Grape fruit	2 (0.7)
Litchi	1 (0.4)
Buckwheat	1 (0.4)
Fig	1 (0.4)
Ginger	1 (0.4)
Mulberry	1 (0.4)
Corn	1 (0.4)
Burdock	1 (0.4)
Cacao	1 (0.4)
Cashew nut	1 (0.4)
Parsley	1 (0.4)
Pistachio	1 (0.4)
Sunflower seed	1 (0.4)

PFAS, pollen-food allergy syndrome.



**Table 4.** Causative foods of PFAS in pollen-sensitized patients

Tree only		Grass only		Weed only	
Foods	No. (%)	Foods	No. (%)	Foods	No. (%)
Apple	42 (60.9)	Pineapple	3 (33.3)	Kiwi	5 (45.5)
Peach	32 (46.4)	Peach	2 (22.2)	Apple	3 (27.3)
Kiwi	25 (36.2)	Kiwi	1 (11.1)	Pineapple	3 (27.3)
Plum	15 (21.7)	Grapes	1 (11.1)	Peach	2 (18.2)
Walnut	14 (20.3)	Taro/tarostem	1 (11.1)	Watermelon	2 (18.2)
Peanut	13 (18.8)	Ginseong	1 (11.1)	Grapes	2 (18.2)
Chestnut	12 (17.4)	Lotus root	1 (11.1)	Tomato	2 (18.2)
Jujube	11 (15.9)	Chestnut	1 (11.1)	Apricot	1 (9.1)
Taro/tarostem	10 (14.5)	Peanut	1 (11.1)	Plum	1 (9.1)
Pear	9 (13.0)	Walnut	1 (11.1)	Melon	1 (9.1)
Cherry	9 (13.0)	Pinenut	1 (11.1)	Korean melon	1 (9.1)
Korean melon	9 (13.0)	Chilli	1 (11.1)	Banana	1 (9.1)
Pine nut	9 (13.0)			Orange	1 (9.1)
Apricot	8 (11.6)			Mandalin	1 (9.1)
Melon	8 (11.6)			Mango	1 (9.1)
Pineapple	8 (11.6)			Potato	1 (9.1)
Tomato	8 (11.6)			Crown daisy	1 (9.1)
Strawberry	6 (8.7)			Pine nut	1 (9.1)
Ginseong	5 (7.3)			Cacao	1 (9.1)
Soy	5 (7.3)				

PFAS, pollen-food allergy syndrome.

Ninety patients (13.9%) showed PFAS to only 1 type of fruit or vegetable, followed by 55 patients (8.5%) to 2, 37 patients (5.7%) to 3, 33 patients (5.1%) to 4, and 82 patients (12.7%) to 5 or more types of foods.

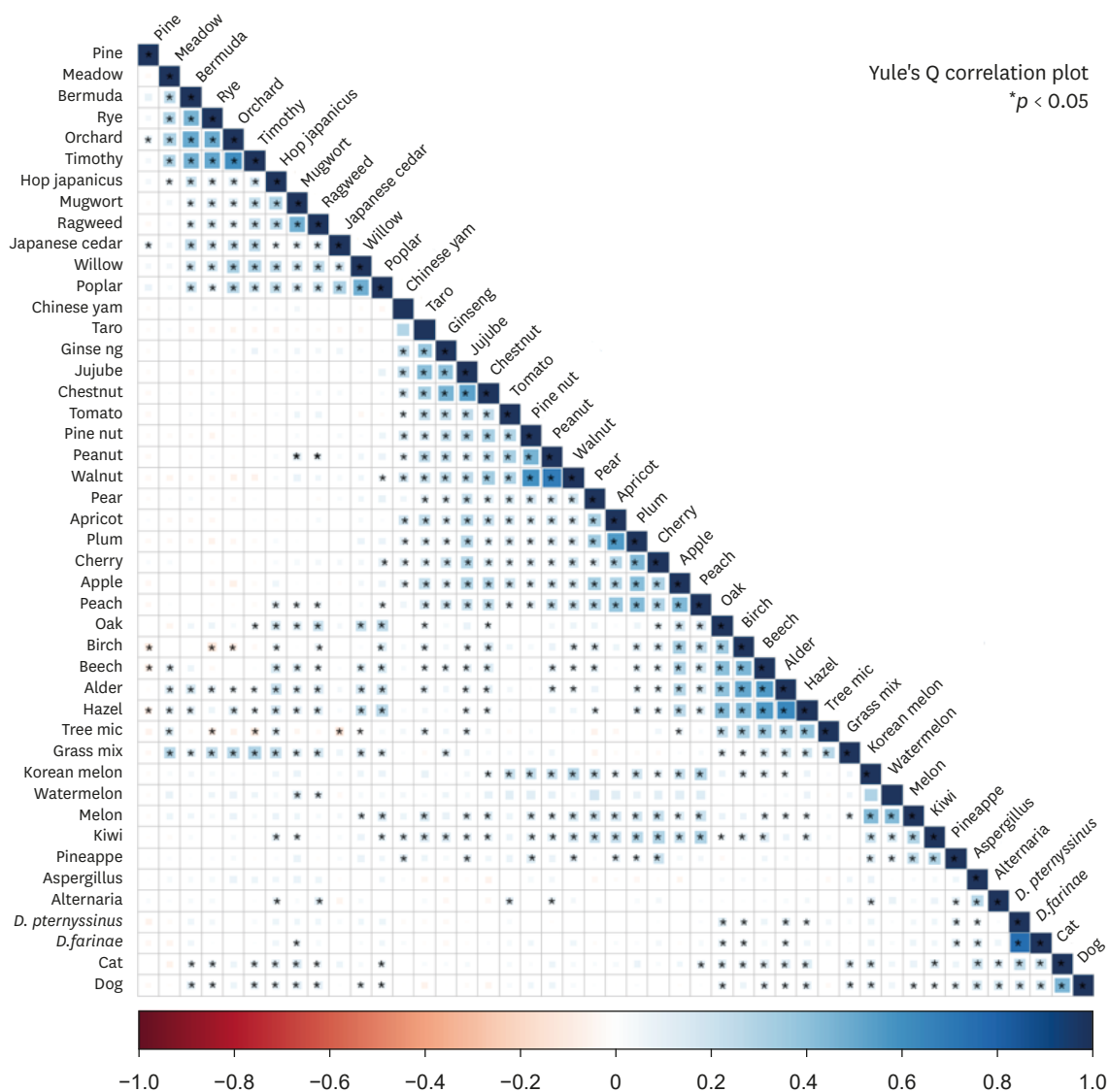
### Associations of causative foods with pollen types

The causative foods according to pollen type are shown in **Table 4** and **Supplementary Table S1**. In patients classified as T ( $n = 174$ ), the causative foods were apple (60.9%), peach (46.4%), kiwi (36.2%), plum (21.7%), walnut (20.3%), peanut (18.8%), chestnut (17.4%), jujube (15.9%), taro/taro stem (14.5%), pear (13%), cherry (13%), Korean melon (13%), pine nut (13%), apricot (11.6%), melon (11.6%), pineapple (11.6%) and tomato (11.6%). Apple and peach were the foods most frequently associated with PFAS in patients classified as T, TG, TW or TGW. Kiwi was the food most frequently associated with PFAS in patients classified as W or GW.

The correlations among inhalant allergens and causative foods are shown in **Fig. 4**. There were significant correlations among Chinese yam, taro, ginseong, jujube and chestnut; pine nut, peanut and walnut; pear, apricot, plum, cherry, apple and peach; and Korean melon, watermelon, melon, kiwi and pineapple ( $P < 0.05$ ). Tree pollens were significantly associated with the Rosaceae family and nuts ( $P < 0.05$ ) as well as chestnut, taro/tarostem, ginseong, jujube, Korean melon, melon and kiwi ( $P < 0.05$ ). Weed pollens were associated with peanut, peach, watermelon and kiwi ( $P < 0.05$ ). These data suggest that cross-allergenicity between pollens and foods is involved in the pathogenesis of PFAS in addition to cross-allergenicity among food types.

## DISCUSSION

This is the first nationwide study of the prevalence and clinical characteristics of PFAS in Korean pollinosis patients. Pollinosis was defined as 1) the presence of AR, AC or BA; and 2) a positive



**Fig. 4.** Correlations among inhalant allergens and causative foods of PFAS. Significant correlations were found among Chinese yam, taro, ginseng, jujube and chest nut; pine nut, peanut and walnut; pear, apricot, plum, cherry, apple and peach; and Korean melon, watermelon, melon, kiwi and pineapple. PFAS, pollen-food allergy syndrome.

response to a pollen allergen by allergy skin test (AST) or serum specific IgE measurement. Previous studies enrolled subjects based on only one of these criteria. Also, we employed questionnaires comprising 44 common foods, and identified several unique and region-specific causative foods not previously implicated in PFAS. Moreover, we compared the clinical characteristics of pollinosis patients with and without PFAS to identify risk factors for PFAS. Finally, we assessed systemic symptoms of PFAS; of the PFAS patients, 8.9% had anaphylaxis.

Among the pollinosis patients, 41.7% had PFAS (42.7% in patients  $\leq 18$  years vs. 40.8% in those  $> 18$  years of age). This is comparable to the prevalence in Western countries,<sup>5,7</sup> but higher than that in Japan.<sup>12,13</sup> Interestingly, the prevalence of PFAS in pediatric pollinosis patients ( $\leq 18$  years of age) was higher than previously reported in Western countries and Japan.<sup>9,14</sup> Three of the PFAS patients were less than 6 years of age, which is unusual.<sup>19</sup> However, 1 study in the United States reported that allergy specialists estimated the

prevalence of PFAS to be 5% in children and 8% in adults, indicating that the prevalence of PFAS is underestimated in clinical practice.<sup>9</sup>

Pollinosis patients with PFAS had higher proportions of females, allergic diseases, and family history of allergic diseases. Patients with PFAS had more severe AR, but the duration of AR was not different. The prevalence of PFAS was significantly positively correlated with the strength of sensitization to birch, oak and mugwort pollen similar to a previous study of birch pollinosis.<sup>4</sup> Therefore, the presence of allergic diseases, family history of allergic diseases, severity of AR and the strength of pollen sensitization are implicated in the development of PFAS in pollinosis patients.

The symptoms of PFAS are not limited to the oropharynx. Indeed, 8.7% of PFAS patients reportedly have systemic symptoms outside the gastrointestinal tract, 3% have systemic symptoms outside the oropharynx, and 1.7% have anaphylactic shock.<sup>9,20</sup> In the present study, the patients exhibited cutaneous (43%), respiratory (20%), gastrointestinal (10.7%), neurologic (4.8%) and cardiovascular (3.7%) symptoms of PFAS. Of the PFAS patients, 8.9% had anaphylaxis. Our results suggest that physicians and patients should be aware of the clinical significance of PFAS and that patients may wish to consider carrying an epinephrine auto-injector.

The most frequent causative foods of PFAS were peach, apple and kiwi (**Table 3**). These were common causative foods in patients classified as T, while kiwi predominated in patients classified as W or GW (**Table 4**). Notably, PFAS to Korean melon was noted in 12.6%. The following local fruits and vegetables were also found to cause PFAS: taro/taro stem (8.9%), ginseong (8.2%), Chinese yam (7%), perilla leaf (4.4%), bellflower root (4.4%), deodeok (3.3%), crown daisy (3.0%), kudzu (3.3%), lotus root (2.6%) and lettuce (1.1%). In Korea, perilla leaf, crown daisy and lettuce are frequently ingested raw, wrapped around rice or pork. Such foods are known as “Ssam” and are popular in Korea. Therefore, these frequent causative foods of PFAS represent Korean eating habits. Moreover, various Korean foods are reportedly implicated in diverse clinical manifestations of PFAS; *e.g.*, bronchospasm and urticaria caused by shiso leaf (*Perilla frutescens*),<sup>21</sup> anaphylaxis by Chinese bellflower root,<sup>22</sup> crown daisy-dependent exercise-induced anaphylaxis,<sup>23</sup> and PFAS caused by celery, lettuce, chicory, radish sprouts, ginseng, mango, kiwi, tomato, crown daisy and perilla leaf.<sup>24-27</sup>

Cross-allergenicity between foods and pollen allergens is linked to the pathogenesis of PFAS.<sup>28</sup> The major allergen of birch pollen, Bet v 1, exhibits cross-reactivity with many food allergens, particularly the Rosaceae family (*e.g.*, apple, peach, pear, cherry, plum and apricot).<sup>29</sup> Bet v 1 is a pathogenesis-related (PR) protein and panallergen present in many plant species. In addition to Bet v 1 homologs, cross-reactive panallergens including profilin, lipid transfer protein and cross-reactive carbohydrate determinants (CCDs) are implicated in PFAS.<sup>2,29</sup> In this study, although we did not identify cross-reactive allergens between foods and pollens, we evaluated the associations between pollen types and culprit foodstuffs. Tree pollens were significantly associated with the Rosaceae family and nuts as well as chestnut, taro/tarostem, ginseong, jujube, Korean melon, melon and kiwi. Weed pollens were associated with peanut, peach, watermelon and kiwi. However, this association could be influenced by tree pollen as 26.4% of PFAS patients were classified as TGW. Further studies are needed to identify the cross-reactive allergens.

This study has several limitations. First, we defined PFAS according to clinical history based on questionnaires and the results of pollen allergy tests. Food-specific IgE levels were not

determined, and provocation tests were not performed. However, oral provocation tests or specific IgE tests may not guarantee true PFAS due to the antigenic lability of commercial antigens. Instead, a careful clinical history can be sufficient to diagnose PFAS. Anhoj *et al.*<sup>30</sup> found that a good clinical history of PFAS to apple had a negative and positive predictive value of 100% and 92%, respectively, compared to the results of food challenge tests. In this study, the diagnosis of PFAS was reliable because allergy specialists took a clinical history using questionnaires and identified positive results of allergy tests by chart review. Secondly, there is a possibility of selection bias because all but two of the institutes were university hospitals; therefore, patients with severe pollinosis may have been included in the study. In addition, recall bias could be accompanied with completion of the questionnaires. Because the questionnaires were based on the self-reporting data, the allergic reactions and symptoms might be exaggerated. However, our results are similar to those of previous reports.

In conclusion, the overall prevalence of PFAS in Korea was 41.7%, and the foods most frequently associated with PFAS were peach, apple and kiwi. Moreover, Korean foods (*e.g.*, taro/taro stem, ginseng, perilla leaf, bellflower root, crown daisy, deodeok, kudzu root and lotus root) were also associated with PFAS, as would be expected in a study performed in Korea. A substantial proportion of the PFAS patients exhibited systemic symptoms including anaphylaxis. Physicians should be aware of the risk of PFAS in pollinosis patients and advise them to avoid the most frequently implicated foods.

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## SUPPLEMENTARY MATERIALS

### Supplementary Table S1

Causative foods of PFAS according to type of pollen

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### Supplementary Fig. S1

Total number of study subjects and prevalence of PFAS according to present residence area (A) and birthplace (B).

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