Food allergy in early childhood increases the risk of pollen-food allergy syndrome

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Abstract

Background: The level of pollen in Korea has increased over recent decades. Research suggests that pollen-food allergy syndrome (PFAS) may be more frequent in childhood than previously recognized. We aimed to investigate the prevalence and characteristics of PFAS in children aged 6–10 years from a general population-based birth cohort. Methods: We analyzed 930 children from the Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) birth cohort. Allergic diseases were diagnosed annually by pediatric allergists. The skin prick tests were performed with 14 common inhalant allergens and four food allergens for children aged 3 and 7 years. Results: Of the 930 eligible children, 44 (4.7\%) aged 6–10 years were diagnosed with. The mean age at onset was 6.74 years. PFAS prevalence was 7.2\% among children with allergic rhinitis (AR) and 19.1\% among those with pollinosis, depending on comorbidity. PFAS was more prevalent in schoolchildren with atopic dermatitis, food allergy, and sensitization to food allergens and grass pollen in early childhood. In schoolchildren with AR, only a history of food allergy before 3 years increased the risk of PFAS (aOR 2.971, 95\% CI: 1.159–7.615). Conclusion: Food allergy and food sensitization in early childhood was associated with PFAS in schoolchildren with AR. Further study is required to elucidate the mechanism by which food allergy in early childhood affects the development of PFAS.

Title page

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Conclusion: Food allergy and food sensitization in early childhood was associated with PFAS in schoolchildren with AR. Further study is required to elucidate the mechanism by which food allergy in early childhood affects the development of PFAS.

Word Count: 224

Key words: Pollen-food allergy syndrome; Prevalence; Children; Birth cohort; Food allergy; Food sensitization; Allergic rhinitis

Key Message
Pollen-food allergy syndrome (PFAS) is a hypersensitivity reaction to specific foods caused by prior sensitization to plant inhalant allergens. The prevalence of PFAS in children aged 6–10 years old was 4.7%. Food allergy and food sensitization in early childhood was associated with PFAS in schoolchildren with allergic rhinitis. Careful monitoring for PFAS symptoms before the age of 6 years is necessary for children with a history of food allergy in early childhood.

Introduction
Pollen-food allergy syndrome (PFAS), also known as oral allergy syndrome (OAS), is a hypersensitivity reaction to specific foods caused by prior sensitization to inhalant pollen allergens. PFAS is triggered by certain fresh (uncooked) fruits and vegetables that cross-react with pollen.1 Global warming has increased the levels of carbon dioxide, nitric oxide, and ozone, which has subsequently caused an increase in the abundance of and sensitization to pollen. The prevalence of asthma, rhinitis, and PFAS is also increasing globally, including in Korea. 2–6

The prevalence of PFAS in patients with pollinosis is approximately 8–63.3% in adults and 5–12.4% in children.1,7,8 A single-center study noted a prevalence of 12.4% in Korean children with pollinosis, while multicenter studies noted a prevalence of 42.7% in patients with allergic rhinitis (AR), allergic conjunctivitis (AC), or asthma.9–11 Studies on the prevalence of PFAS typically investigated populations with AR or inhalant allergens sensitization, which may have caused an overestimation of prevalence.12 However, studies on the prevalence of PFAS in the general population are lacking, and there have only been two cross-sectional cohort studies in Danish adults and Japanese adolescents.13,14

AR patients with PFAS had a higher prevalence of additional allergic comorbidities, especially anaphylaxis, urticaria, asthma, and atopic dermatitis (AD) compared with those without.15 Additionally, atopic adults with PFAS had a higher prevalence of rhinoconjunctivitis, asthma, and chronic urticaria than atopic adults without PFAS.16 Although these studies investigated comorbidities in high-risk patients, few have assessed the general population or analyzed the relationship between PFAS and allergic diseases longitudinally.13,14

Therefore, we aimed to investigate the prevalence of PFAS in the general population aged 6–10 years. We assessed clinical characteristics including pollen sensitization, trigger foods, and risk factors for PFAS by
analyzing sensitization and comorbidities in early childhood from a general population-based birth cohort study.

Materials and Methods

Study population

The COhort for Childhood Origin of Asthma and Allergic diseases (COCOA) is a prospective, general population-based birth cohort study designed to investigate the individual and interactive effects of genetics, perinatal environment, maternal lifestyle, and psychosocial stress of mother and child on pediatric susceptibility to allergic diseases. Regular follow-up visits involving physician examination and self-report questionnaires concerning the environment were conducted at least 26 weeks gestation, at birth, 6 months, 1 year, and then annually. From yearly follow-ups of pediatric allergists, we collected information on the allergic symptoms, diagnosis, and prescribed treatment. Among the 3,102 pairs enrolled in the COCOA cohort, 1,636 children were aged over 6 years. The 706 patients lacking clinical and laboratory data were excluded, leaving 930 patients to be analyzed (Figure E1). The average age of the patients was 8.02 years, and 52.7% were male. Significant differences in birth weight, breastfeeding rates, and antibiotic use before 1 year of age were observed between the included and excluded groups (Table E1).

Allergic diseases including PFAS were diagnosed by a physician or typical symptoms (itching, sore throat, or swelling) in the lips, mouth, and throat immediately after eating fresh fruits or vegetables by parental questionnaire. If PFAS was suspected, the trigger of PFAS was also investigated.

The study was approved by the Institutional Review Boards of Asan Medical Center (IRB No. 2008–0616), Samsung Medical Center (IRB No. 2009-02-021), Severance Medical Center (IRB No. 4-2008–0588), CHA Gangnam Medical Center (IRB No. 2010–010), and Seoul National University Hospital (IRB No. H-1401-086-550) before initiation. Written informed consent was obtained from each patient’s parents or guardians before the interview, confirmed by each IRB.

Specific IgE to egg white and milk

Serum levels of specific IgE to egg white and milk at 1 and 3 years of age were determined using the Immuno-CAP (Thermo Fisher Scientific, Waltham, MA, USA) system.

Skin prick tests (SPTs)

SPTs were performed for the 14 most common inhalant allergens (Allergopharma GmbH & Co, Reinbek, Germany), including *Dermatophagoides pteronyssinus* (Der p), *Dermatophagoides farina* (Der f), dog dander, cat epithelium, cockroach, *Alternaria alternata*, *Aspergillus fumigatus*, grass pollen mixture, alder, birch, oak, ragweed, mugwort, alder, and four food allergens, including peanuts, egg whites, cow’s milk, and soybeans at 3 and 7 years of age. Histamine (10 mg/mL) was used as the positive control, and normal saline was used as the negative control. A mean wheal size of 3 mm or larger for allergens and histamine after 15 minutes was considered a positive result. Atopy was defined as the presence of one or more positive test results to any of the 18 allergens assessed using SPTs.

Statistical analysis

Data are presented as means and standard deviations or numbers and percentages. Data were analyzed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Comparisons between the PFAS and non-PFAS groups were calculated using the Pearson chi-square test or independent t-test as appropriate. Unadjusted and multivariable-adjusted logistic regression models examined associations between PFAS and allergic disease in early childhood. Candidate variables for adjustment included sex, delivery mode, gestational age, parental history of allergic diseases, maternal education level, exclusive breastfeeding during the first 6 months of life, and antibiotic treatment during the first 1 year of life were used to calculate the odds ratio and 95% confidence interval. A P-value of <0.05 was considered statistically significant.

Results
1. Clinical characteristics of the study population and prevalence of PFAS

Of the 930 children, 44 (4.7%) had PFAS, and the mean age of onset was 6.74 years (Table 1). The mean age of the PFAS group was older than that of the non-PFAS group, whereas the rate of breastfeeding was significantly higher in the non-PFAS group compared with the PFAS group. The prevalences of AR and AC in the study population were 48.9% and 16.5%, respectively (Figure 1). Pollen sensitization rate of the study population was 11% (Figure 1) and common in birch, oak, and alder (in order of frequency). Depending on comorbidity, the prevalence of PFAS was 7.2% among children with AR and 19.1% among children with pollinosis (Figure E2).

2. Causative foods

Foods triggering PFAS in Korean children in order of prevalence were: fruit (47.7%), vegetables (27.3%), and nuts (9.1%) (Table 2). Among fruits, kiwi (22.7%) and peach (11.4%) were the most common causes of PFAS.

3. Comorbidity of allergic diseases and sensitization in schoolchildren with PFAS

Children with PFAS were more likely to be diagnosed with AR and AD compared with those without PFAS (75.6% vs. 47.6%, p = 0.001; 31.7% vs. 15.9%, p = 0.016) (Table 1). There was no significant difference in prevalence of asthma between the PFAS group and non-PFAS group (7.3% vs. 5.0%, p = 0.461).

Patients aged 7 with PFAS showed a significantly higher sensitization rate during the skin prick test to birch (34.4%), alder (12.5%), Hop J (12.5%), oak (18.8%), and ragweed (6.3%) than those without PFAS (Figure 2). However, there was no significant difference between the two groups in the sensitization to food allergens (data not shown), indoor allergens such as Der f, Der p, and dog, or other outdoor allergens, such as Alternaria.

4. Association between PFAS and allergic diseases or sensitization in early childhood

PFAS was associated with food allergy (adjusted odds ratio [aOR], 3.803; 95% confidence interval [CI]: 1.795–8.057) and AD at age 1–3 years (aOR, 2.393; 95% CI: 1.243–4.609) (Table 3). Sensitization to milk or egg white in serum-specific IgE at 1 year and sensitization to food allergens in the skin prick test performed at age 3 years were risk factors in the development of PFAS in schoolchildren (Table 3). However, there was no significant association between PFAS and AR or recurrent wheeze between children aged 1–3 years (Table 3).

Among children with PFAS, sensitization rate to egg (14.3%), milk (5.6%), peanut (5.6%), and grass (5.6%) at age 3 years was higher in children with PFAS than those without PFAS (Table E2).

5. Association between PFAS and allergic diseases or sensitization in early childhood among school children with AR

Among children with AR, PFAS was significantly associated with food allergy in early childhood (aOR, 2.971; 95% CI: 1.159–7.615) and was not associated with AD, AR, and recurrent wheeze (Table 4). Sensitization to milk or egg white in serum-specific IgE at 1 year of age and sensitization to milk, egg, or peanut at age 3 years were risk factors in the development of PFAS in schoolchildren with AR.

Discussion

The prevalence of PFAS in Korean children aged 6–10 years was 4.7%, and the mean age of onset was 6.74 years. Kiwi, tomato, and peach were the most common triggers of PFAS. Food allergy, AD, and sensitization to foods in early childhood were associated with the development of PFAS in schoolchildren. Sensitization to inhalant allergens at 3 years did not increase the risk of school-age PFAS. Therefore, sensitization to food antigens and food allergy in early childhood was related to PFAS in schoolchildren, particularly in those with AR. To the best of our knowledge, this is the first general population-based cohort study that demonstrates the association between allergic diseases in early childhood and PFAS.
Most studies on the prevalence of PFAS have focused on high-risk patients who visited hospitals for treatment or suffered from allergic diseases, recording a prevalence of 4.7% to more than 20% in children and 13–58% in adults.\textsuperscript{12,21,22} In Korea, a multicenter cross-sectional study reported a PFAS prevalence of 42.7% in children with pollinosis.\textsuperscript{9} However, there is a possibility that prevalence in high-risk populations is overestimated compared with the general population. In addition, the diversity of risk factors directly affected prevalence, so these results are difficult to generalize or compare against other studies. Only two cross-sectional studies were conducted to investigate PFAS in the general population cohort. A Danish study has reported a PFAS prevalence of 16.7% in young adults, which was lower than 20.5% in other European studies conducted in adolescents and adults with AR, or 23.0% in children with risk factors.\textsuperscript{13,15} A Japanese study in the general population also reported that 11.7% of adolescents had PFAS, and 22.9% with pollen allergy had PFAS.\textsuperscript{14} Thus, the lower prevalence of PFAS (4.7%) in this study likely results from the general population and younger age of the participants compared with other studies.

Most studies on PFAS were cross-sectional observational studies intending to identify an association between PFAS and other risk factors. In an Italian study on pollen-induced AR, longer AR duration was associated with PFAS.\textsuperscript{21} Additionally, the prevalence of asthma was significantly higher in patients with birch-sensitization and PFAS than in those without PFAS. There was also no significant difference in the prevalence of other allergic diseases such as AD rhinoconjunctivitis according to the presence of PFAS.\textsuperscript{16} These studies analyzed the comorbidities at the time of investigation; therefore, it is difficult to determine the relationship between PFAS and sensitization or allergic diseases in early childhood. In this study, children were followed-up longitudinally from birth so that the association between the development of PFAS and allergic conditions could be thoroughly assessed. There were significant differences in AD, food sensitization, and food allergy in early childhood between the PFAS and non-PFAS groups. In particular, food sensitization and food allergy in early schoolchildren with AR remained significant risk factors for PFAS. These findings suggest that AR children with food allergy in early childhood are more susceptible to PFAS than AR children without food allergy history. Therefore, monitoring PFAS symptoms is necessary in children with a history of food allergy or sensitization in early childhood.

Class II food allergens are the primary concern in children with PFAS. The food allergen itself is not typically the primary sensitizer, as observed in class I food allergens.\textsuperscript{12} In general, class I food allergens are stable in heat and during digestion,\textsuperscript{12} allowing them to retain their immunoglobulin E (IgE)-binding conformation, potentially leading to an increased ability to sensitize and a higher incidence of severe systemic reactions.\textsuperscript{12} In this study, sensitization to class I food allergens in early childhood and a history of food allergy were proven risk factors for school-age PFAS. Additionally, despite the varying characteristics of food antigens and sensitization pathways, mucosal immunity defects may be associated with food allergy and PFAS. Further research is needed to elucidate the mechanisms of PFAS.

The age at which food reactions begin, including PFAS, has been reported to be 25 years in a single study conducted on adults using questionnaires in the UK.\textsuperscript{23} In this study, the mean age of onset of PFAS was 6.74 years (3–10 years). Therefore, monitoring for PFAS is necessary in children aged under 6 years.

Kiwi, peach, tomato, and watermelon were the common causative foods in this study, which are associated with birch antigens (Bet V1 and Bet V2), the most common cause of pollen sensitization.\textsuperscript{24} Another Korean study revealed that apple, peach, and kiwi were common causative foods for children aged 2–6 years with AD and birch sensitization.\textsuperscript{25} In Western countries, 60–90% of patients with pollinosis exhibit PFAS symptoms;\textsuperscript{26,27} however, they were observed in only 41.7% of patients with pollinosis in a Korean multicenter study,\textsuperscript{9} and 19.1% of children in this study. In Western countries, pollinosis from Poaceae, such as birch and timothy grass, and Asteraceae, such as ragweed and mugwort, are common given their cross-reactions with many foods. The incidence of PFAS varies depending on the environment, plant cultivation circumstances, ethnic groups, and regional differences,\textsuperscript{7} suggesting the difference in prevalence between Korea and Western countries.

This study had several limitations. First, the number of children with PFAS in this general population-based cohort study was relatively small compared with other high-risk population studies. Second, PFAS was
diagnosed using a questionnaire and physician’s diagnosis, and a food provocation test was not performed. However, PFAS was diagnosed through reference of detailed medical history noted by pediatric allergists. Despite these limitations, this study is the first to investigate PFAS prevalence in young children in the general population. Moreover, as a birth cohort study, longitudinal analysis was possible based on acquisition of various clinical data before the development of PFAS. Novel associations between PFAS and FA or food sensitization have been revealed, and further studies are warranted to expand on this new perspective on PFAS.

In conclusion, PFAS occurs in 4.73% of children aged 6–10 years, and the most common causative food is fruit, especially kiwi. The risk of developing PFAS in schoolchildren increased in the presence of food allergy or food sensitization in early childhood. Further studies to investigate the association of food allergy in early childhood with the development of PFAS is required.

Author contribution
Kun Baek Song: Investigation, Data curation, Formal analysis, Writing - original draft, Visualization
Min Jee Park, Eom Ji Choi, Sungsu Jung, Jisun Yoon, Hyun-Ju Cho: Writing – review & editing, Validation
Bong Seong Kim, Kangmo Ahn, Kyung Won Kim, Youn Ho Shin, Dong In Suh: Conceptualization, Investigation, Resources
Soo-Jong Hong, So-Yeon Lee: Funding acquisition, Conceptualization, Investigation, Resources, Supervision, Writing – review & editing

References


**Table 1. Clinical characteristics of all children**

<table>
<thead>
<tr>
<th></th>
<th>PFAS (n=44, 4.7%)</th>
<th>Non-PFAS (n=886, 95.3%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td>8.48 ± 1.3</td>
<td>8.00 ± 1.3</td>
<td>0.016</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>50.0</td>
<td>52.8</td>
<td>0.758</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>6.74 ± 1.6</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Data presented as mean ± SD (range) or number (%).

P-values for comparing the PFAS and non-PFAS groups were calculated using the Pearson chi-square test or independent t-test as appropriate. IgE = immunoglobulin E, PFAS = pollen-food allergy syndrome, SD = standard deviation.

### Table 2. Food triggers of pollen food allergy syndrome

<table>
<thead>
<tr>
<th>Food</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kiwi</td>
<td>10</td>
<td>22.7</td>
</tr>
<tr>
<td>Peach</td>
<td>5</td>
<td>11.4</td>
</tr>
<tr>
<td>Pineapple</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Orange</td>
<td>2</td>
<td>4.6</td>
</tr>
<tr>
<td>Mango</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Nuts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peanut</td>
<td>3</td>
<td>6.8</td>
</tr>
<tr>
<td>Hazelnut</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Pine nut</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Vegetables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tomato</td>
<td>8</td>
<td>18.2</td>
</tr>
<tr>
<td>Watermelon</td>
<td>4</td>
<td>9.1</td>
</tr>
<tr>
<td>Oriental melon</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Paprika</td>
<td>1</td>
<td>2.3</td>
</tr>
<tr>
<td>Cucumber</td>
<td>1</td>
<td>2.3</td>
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</table>

### Table 3. Multivariate analysis of pollen food allergy syndrome according to allergic diseases and sensitization to allergens in early childhood

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>0.894</td>
<td>0.313-2.559</td>
<td>1.301</td>
<td>0.418-4.049</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>2.996</td>
<td>1.622-5.534</td>
<td>2.789</td>
<td>1.292-6.017</td>
</tr>
</tbody>
</table>
Table 4. Effect of allergic disease in early childhood on pollen-food allergy syndrome in children with allergic rhinitis.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic rhinitis</td>
<td>0.608</td>
<td>0.179–2.066</td>
<td>0.539</td>
<td>0.153–1.899</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>1.832</td>
<td>0.880–3.815</td>
<td>1.594</td>
<td>0.716–3.549</td>
</tr>
<tr>
<td>Food allergy</td>
<td>3.356</td>
<td>1.402–8.033</td>
<td>2.971</td>
<td>1.150–7.615</td>
</tr>
<tr>
<td>Recurrent wheeze</td>
<td>1.129</td>
<td>0.378–3.376</td>
<td>1.348</td>
<td>0.427–4.253</td>
</tr>
<tr>
<td>Sensitization(^a) to milk or egg white (specific IgE) at age 1 year</td>
<td>2.536</td>
<td>1.065–6.041</td>
<td>3.164</td>
<td>1.006–9.957</td>
</tr>
<tr>
<td>Sensitization(^b) to food allergens (SPT) at age 3 years</td>
<td>23.114</td>
<td>3.669–145.598</td>
<td>26.342</td>
<td>1.768–392.555</td>
</tr>
<tr>
<td>Sensitization(^b) to inhalant allergens (SPT) at age 3 years</td>
<td>1.300</td>
<td>0.500–3.380</td>
<td>1.458</td>
<td>0.430–4.943</td>
</tr>
</tbody>
</table>

\(^a\) Specific IgE \(\geq 0.35\) IU/mL

\(^b\) Allergen histamine ratio \(\geq 1\)

aORs and 95% CIs obtained from logistic regression analysis adjusted for sex, parental history of allergic disease, maternal education level, delivery type, breastfeeding. aORs = adjusted odds ratios.
Specific IgE [?]0.35 IU/mL.  

Allergen histamine ratio [?]1.

Figure Legends

Figure 1. Prevalence of allergic disease and characteristics of study participants aged 6–10 years.

Figure 2. Comparison of sensitization to inhalant allergens at 7 years of age between pollen-food allergy syndrome and controls. P-values for the comparison between the PFAS and non-PFAS groups were calculated using the Pearson chi-square test, PFAS = pollen-food allergy syndrome.

* P <0.05.

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