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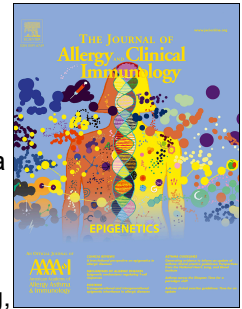
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Food aversion and poor weight gain in food protein-induced enterocolitis syndrome: a retrospective study

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Clinical Implication: FPIES patients with multiple food triggers or induced by cow's milk and banana are at risk of food aversion and poor body weight gain respectively.

Capsule summary: FPIES with multiple food triggers increased the risk of food aversion while FPIES to cow's milk and banana increased the risk of poor body weight gain.

Key words: food protein-induced enterocolitis syndrome; food aversion; poor body weight gain.

Abbreviation:

CI: Confidence interval

EMR: Electronic medical record

FPIAP: Food protein-induced allergic proctocolitis

FPIES: Food protein-induced enterocolitis syndrome

IBD: Inflammatory bowel diseases

IgE: Immunoglobulin E

IQR: Interquartile range

OFC: Oral food challenge

OR: Odds ratio

RPDR: Research patient data registry

SD: Standard deviation

Abstract

Background: Food protein-induced enterocolitis syndrome (FPIES) is a form of non-IgE mediated gastrointestinal food allergy. Insufficient data exist in regards to gastrointestinal history and outcome, particularly comorbidity, family history, food aversion, and poor body weight gain.

Objective: To identify the gastrointestinal outcomes and related risk factors in FPIES.

Methods: We analyzed the clinical features and gastrointestinal outcomes of FPIES patients retrospectively at four hospitals in Boston.

Results: Two hundred and three FPIES patients were identified, including 180 only with acute FPIES, 8 with chronic FPIES, and 15 with both. Oat (34.5%), rice (29.6%), and cow's milk (19.2%) were the most common food triggers. The prevalence of personal history with allergic proctocolitis (23.2%) and family history with inflammatory bowel diseases (9.4%) and celiac disease (7.3%) were higher than the general population. Compared to the FPIES patients triggered by 1 or 2 foods, the risk of developing food aversion increased in cases triggered by 3 or more foods (adjusted odds ratio (OR) = 3.07 [95% confidence interval (CI), 1.38 – 6.82], $P = .006$). The risk of poor body weight gain increased in FPIES triggered by cow's milk (adjusted OR = 3.41 [95% CI, 1.21 – 9.63], $P = .02$) and banana (adjusted OR = 7.63, [95% CI, 2.10 – 27.80], $P = .002$).

Conclusion: Gastrointestinal comorbidities and family history were common in FPIES patients. FPIES patients with 3 or more triggers were at risk of food aversion. Patients with cow's milk and banana triggered FPIES were at risk of poor body weight gain.

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a unique form of non-IgE mediated food allergy. Patients with acute FPIES typically have profuse repetitive vomiting 1 to 4 hours after the ingestion of a trigger food. The severity of acute FPIES varies, and severity-based management has been proposed.¹ Chronic FPIES in young infants is triggered by foods fed daily, presenting as intermittent but progressive vomiting and diarrhea. FPIES is slightly more common in male children.²⁻⁴ Cow's milk and soy are the most common trigger foods reported in the United States,^{2,4} but recently, in Texas, grains were reported as the leading trigger.⁵ As for adult-onset FPIES, shellfish is the most common trigger food, occurring more commonly in females.^{6,7}

The diagnosis of FPIES is challenging and many diseases need to be excluded before the accurate diagnosis is made. For acute FPIES, a diagnostic criterion has been proposed, and an oral food challenge (OFC) is not necessary if the typical symptoms present repeatedly.¹ The diagnosis of chronic FPIES still depends on a confirmatory OFC or an acute reaction after reintroduction. Without an OFC or acute reaction, the diagnosis of chronic FPIES is presumptive.¹

Children with FPIES are at risk of nutritional deficiency, poor body weight gain,

and feeding difficulties. These are thought to be related to diet restriction and/or lack of adequate solid food introduction due to parental anxiety. However, their relationship to diet has never been reported. Early involvement of nutritionists is necessary and commonly used in clinical practice.⁸ While FPIES patients are commonly documented to have other allergic diseases or atopic family history,³⁻⁵ personal or family histories of gastrointestinal diseases in FPIES patients are seldom mentioned in literature. We therefore sought to quantitatively examine the relationship between FPIES and gastrointestinal and nutritional health.

In this study, we undertook a multi-hospital, retrospective review of FPIES cases to systemically analyze demographics, clinical presentation, history of gastrointestinal disease, and family history as well as investigate risk factors for developing food aversion and poor body weight gain.

Methods

Study design

We retrospectively reviewed FPIES cases in 2 tertiary hospitals (Massachusetts General Hospital and Brigham and Women's Hospital) and 2 community hospitals (North Shore Medical Center and Newton-Wellesley Hospital) in the Boston-based Partners HealthCare system. FPIES patients were identified through the Research Patient Data Registry (RPDR), using the ICD-10 code K52.21 (food protein-induced enterocolitis syndrome), as well as an electronic medical record (EMR) keynote query searching for the keyword, food protein-induced enterocolitis syndrome or FPIES, from outpatient, inpatient, and emergency departments visits, seen from November 5, 1991, to December 31, 2018. This study was approved by the Partners IRB (Protocol 2018P002222).

FPIES case definition

All of the records identified by the RPDR system were manually reviewed. The diagnosis of acute FPIES was made following criteria in the international consensus guidelines (Table E1).¹ For the diagnosis of chronic FPIES, all included cases had intermittent but progressive vomiting when the trigger food was still in the diet. The vomiting subsided within days after the elimination of the trigger. Confirmed chronic

FPIES cases indicate those with vomiting 1 to 4 hours after reintroduction of the trigger food, and the rest of the cases were enrolled into the analysis as a presumptive chronic FPIES case.¹ Uncertain acute or chronic FPIES cases were reviewed by at least two authors before inclusion in the analysis.

Adult-onset FPIES cases were categorized as patients whose earliest age at onset of FPIES symptoms was at 18 years of age or older. The diagnosis of adult-onset FPIES followed the acute FPIES criteria in the international consensus guidelines.¹ Food poisoning, acute gastroenteritis, and other diseases causing vomiting or diarrhea were excluded before the diagnosis was made. Multiple-trigger FPIES cases were defined as patients who reacted to 3 or more different foods. The resolution of FPIES was defined by one of the two criteria: passing an OFC or introducing the trigger food at home without FPIES symptoms.

Data collection

Using EMR notes, we collected demographic and clinical data including the age of onset, age of resolution, symptoms, and trigger foods. We collected mode of delivery, gestational age, breastfeeding, comorbidity, past history, and family history. We specifically collected family history on inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis. A family history of celiac disease was based on

physicians' notes, excluding gluten sensitization or gluten intolerance.

Patients with atypical FPIES were those with documented IgE-sensitization to the trigger foods, either by skin prick tests or by blood tests. Of FPIES cases who included any mention of food allergy, concomitant IgE-mediated food allergy was diagnosed by convincing IgE-mediated food allergic symptoms along with positive allergy tests or by histories of anaphylaxis.

Poor body weight gain was defined by body weight below the 3rd percentile for age and gender presented at least two separate measurements without any contributing reasons other than FPIES. Food aversion was defined as patients with reluctance, avoidance, or fear of eating or drinking, which was documented by pediatric gastroenterologists in EMRs.

The severity of an acute FPIES episode was determined according to the international consensus guideline.¹ During a mild episode, patients had 1-2 episodes without lethargy. Patients with moderate or severe episodes were defined as having 3 or more episodes of vomiting: a moderate case had mild lethargy and a severe case had severe lethargy, cyanosis, hypotonia, or unresponsiveness to stimulus.

Statistical analysis

We reported non-parametric demographic and clinical data as medians (interquartile range [IQR]) and parametric data as means $\pm$ standard deviation (SD). For

comparison of percentage or proportion, Chi-square test or Fisher's exact test was used depending on the expected cell sizes. Mood's median test and the independent t-test were used to compare the median and mean between two groups. The heatmap of the correlation between different trigger foods was illustrated using an R package "corrplot".⁹ The phi coefficient was used to measure the association between 2 different trigger foods in all 203 FPIES patients. Phi coefficient equal or more than +.70 was categorized as a very strong association, between +.40 to +.69 as a strong association, +.30 to +.39 as moderate, +.16 to +.29 as weak, and equal or less than +.15 as no or negligible association. The backward conditional method was used in multivariate logistic regression analysis. Time-to-resolution outcome was analyzed by the Kaplan-Meier estimator, and the resolution distribution between the typical and atypical FPIES groups was compared by the log-rank test. The above statistical analyses and the survival curve generation were performed with IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA).

Results

Subjects' characteristics

From 5,112,203 electronic medical records, we identified 875 unique records on the initial query of the RPDR system. From these, we identified 203 FPIES cases. The remaining records were excluded from analysis because they were falsely matched or compatible with other diseases. Two hundred and one (99.0%) patients were seen at least once at Massachusetts General Hospital, 83 (40.9%) at Newton-Wellesley Hospital, 63 (31.0%) at Brigham and Women's Hospital, and 24 (11.8%) at North Shore Medical Center. One hundred and ninety-four (95.6%) FPIES cases were confirmed after a referral. Only 9 cases were identified during the follow-up visits for IgE-mediated food allergy in the Partners HealthCare system.

Of 203 FPIES cases, 180 had only acute FPIES and 8 only had chronic FPIES. Of the 15 with both acute and chronic FPIES, 8 experienced acute FPIES symptoms following the reintroduction of the foods that had triggered chronic FPIES and 7 had different trigger foods to acute and chronic FPIES. We identified 17 adult-onset FPIES cases, all of whom were acute FPIES cases.

In this cohort, 52.7% were male and 85.7% were identified as white (Table I). We found 23.2% of patients with a past medical history of physician-diagnosed food protein-induced allergic proctocolitis (FPIAP), 23 cases (11.3%) with IgE-mediated

food allergy, and 82 (40.4%) with eczema.

In this study, the FPIES patients had a higher probability of a family history of IBD (9.4%) or celiac disease (7.3%), compared with published data (in the general population of North American, the prevalence of IBD¹⁰ and celiac disease¹¹ are 0.6% and 0.75% respectively). Three FPIES patients had a family history of FPIES (2 siblings and 1 cousin). The characteristics of the FPIES cases were shown in Table I.

The median ages of onset and diagnosis in 203 cases were 6.0 (IQR, 4.5 – 9.0) and 10.0 (IQR, 7.0 – 21.5) months respectively (Figure E1). In the pediatric FPIES cohort, the median ages of onset and diagnosis were 6.0 (IQR, 4.5 – 8.0) and 9.0 (IQR, 6.6 – 15.0) months. In the adult-onset FPIES cases, the median ages of onset and diagnosis were 33.0 (IQR, 22.1 – 46.3) and 45.0 (IQR, 35.0 – 51.0) years (Figure E2).

The age of onset in 88.2% of the FPIES cases was below 2 years. The median ages of onset of chronic and acute pediatric FPIES patients were 0.4 (IQR, 0.0 – 1.7) and 6.0 (IQR, 5.0 – 7.0) months respectively. In Figure E3, we demonstrated the ages of onset and diagnosis from patients younger than 2 years of age. The major peak of onset age occurred at 6 months of age, with a minor one soon after birth, which was consistent with the onset ages of acute and chronic FPIES.

Trigger foods

Overall, oat was the most common trigger food (34.5%), followed by rice

(29.6%) and cow's milk (19.2%) (Figure 1). Specifically for acute FPIES, oat was still the most common trigger (70 of 195, 35.9%, Figure E4) while for chronic FPIES, cow's milk was the most common trigger (20 of 23, 87.0%). Five chronic FPIES cases were triggered by soy, and more interestingly, two of them were triggered by rice from the rice cereal used to thicken infant formula. 133 of 203 (65.5%) cases had FPIES reaction on their first ingestion. The percentage developing FPIES reaction on their first ingestion by different triggers was similar except that 37 of 39 (94.9%) FPIES cases triggered by milk had an FPIES reaction on their first ingestion (94.9% vs. 65.5%, $P < .001$).

We found chicken and turkey had a strongly positive association while wheat and barley had a moderately positive association (Figure 2; phi coefficients were +.44 and +.31 respectively, both P values $< .01$). Cow's milk and soy, shellfish and fish, and avocado and banana were weakly associated (phi coefficient +.21, +.18, and +.17, all $P < .05$).

In 37 (18.2%) cases, multiple (≥ 3) triggers were documented (Figure E5, Table E2). Compared to FPIES cases with two or fewer triggers, patients with multiple triggers were more likely to develop food aversion (43.2% vs. 16.9%, $P < .001$) and to have poor body weight gain (21.6% vs. 6.6%, $P = .005$). The patients with multiple triggers frequently reacted to egg, soy, grains (oat, rice, wheat, and

barley), vegetable (sweet potato, legume), fruits (avocado, banana), and turkey, but were less likely to have shellfish-related FPIES (all P values $< .05$, Figure E6).

Risk Factors for Food Aversion and Poor Body Weight Gain

Compared to FPIES cases without food aversion, patients with food aversion were more likely to have multiple triggers (36.4% vs. 14.2%, $P = .001$), have a wheat trigger (13.6% vs. 2.1%, $P = .002$), and have a family history of food allergy (45.4% vs. 28.4%, $P = .04$) (Table II). Compared to cases with normal weight gain, those with poor weight gain was associated with chronic FPIES (31.6% vs. 10.2%, $P = .008$), multiple triggers (42.1% vs. 16.8%, $P = .008$), and triggers of cow's milk (42.1% vs. 18.6%, $P = .02$) and banana (26.3% vs. 5.4%, $P = .001$) (Table II).

Cow's milk as the FPIES trigger was associated with chronic FPIES, and banana was associated with multiple-trigger FPIES (both $P < .001$). By multivariate logistic regression analysis, the poor body weight gain was correlated to FPIES triggered by cow's milk (adjusted odds ratio (OR) = 3.41 [95% confidence interval (CI), 1.21 – 9.63], $P = .02$) and banana (adjusted OR = 7.63, [95% CI, 2.10 – 27.80], $P = .002$), not correlated to chronic FPIES or multiple trigger (Table III).

By multivariate logistic regression analysis, we found that FPIES triggered by multiple foods was the only risk factor for the development of food aversion (adjusted OR = 3.07 [95% CI, 1.38 – 6.82], $P = .006$). With each additional trigger food, the

risk of developing food aversion increased by 1.65 times ([95% CI, 1.19 – 2.29], $P = .003$). The logistic regression results are summarized in Table III.

Symptoms, Severity, and Management

The mean onset of symptoms was 2.4 hours after food ingestion (SD $\pm$ 1.0 hours). The onset time was significantly longer after eating shellfish (mean $\pm$ SD, 3.5 $\pm$ 1.8 hours, $P < .001$) and egg (mean $\pm$ SD, 3.1 $\pm$ 0.8 hours, $P = .01$).

Of 195 acute FPIES patients, all met the major criterion of 2017 consensus guidelines, vomiting in 1 to 4 hours after ingestion of the food without classic IgE-mediated symptoms. Of these, 156 (80.4%) had repetitive episodes of vomiting after eating the same food, and 139 (71.6%) presented with lethargy during an FPIES reaction. The rest of the features in the acute FPIES cases were summarized in Figure 3A.

Among 23 chronic FPIES cases, all presented with persistent and repetitive vomiting, which subsided after the offending food was eliminated from the diet. Chronic diarrhea and at least one bloody stool were documented for 14 (61%) and 12 (52%) of those patients. Additional features in these chronic FPIES cases were summarized in Figure 3B.

In the 2017 consensus guidelines,¹ the severity of acute FPIES episodes was categorized as mild, moderate, or severe based on symptoms and management. We

reviewed 500 documented acute FPIES episodes and found 132 (26.4%) mild episodes, 308 (61.6%) moderate episodes, and 60 (12.0%) severe episodes.

Regarding the management of acute FPIES episodes, 74.1% of events were treated at home with oral hydration, 23.0% managed in the emergency departments, and 2.9% required admission to the hospital or to the intensive care units. Regarding the management of chronic FPIES episodes, 56.5% of events were treated at home, 17.4% in the emergency department, and 21.7% required admission. Chronic FPIES patients had a higher probability to be admitted to the hospital or the intensive care units ($P = .002$)

Adult-onset FPIES

We identified 17 cases who experienced their first episode of acute FPIES after 18 years of age, and none of them presented as chronic FPIES. 15 of 17 (88.2%) were female. The majority of patients ($n = 16$) were Caucasian, and one was African-American. Among the 17 adult-onset FPIES cases, 14 (82.4%) were triggered by fish or shellfish, 1 by legumes, 1 by broccoli and zucchini, and 1 by turkey and chicken. All adult-onset FPIES cases tolerate their triggers before the onset of acute FPIES. The severity of the adult-onset FPIES was milder: none of the adult-onset FPIES episodes was severe while in pediatric FPIES cases, 60 of 458 (13.1%) episodes were severe ($P = .01$). Adult-onset FPIES was less frequently associated

with lethargy, diarrhea, and visits to the emergency department ($P < .05$, Figure E7).

Abdominal pain was only reported in 2 (11.8%) adult-onset FPIES patients, which was less frequently than found in a previous study (90%; 18/20).⁶ One adult-onset FPIES case had repetitive vomiting, shivering, and hypothermia, requiring intravenous rehydration in an emergency department.

Atypical FPIES and IgE-mediated food allergy

Of 203 FPIES cases, 149 were tested by skin prick or serum assay for IgE sensitization, and 24 atypical FPIES cases were identified. Fifteen of 24 atypical FPIES cases were demonstrated by skin prick tests, 3 by blood tests, and 6 by both. The most common food related to atypical FPIES was egg (7/24, 29.2%), followed by cow's milk (6/24, 25.0%). During follow-up, 9 of 24 atypical FPIES cases developed IgE-mediated food allergy (5 to egg, 4 to cow's milk, 3 to peanut, 2 to tree nut, and 1 to wheat; 4 of them had IgE-mediated food allergic reactions to more than 1 food).

In this study, a total of 23 patients had concomitant IgE-mediated food allergy, 9 before and 14 after the onset of FPIES. The most common IgE-mediated food allergen was peanut and egg (each with 8 cases [34.8%]), followed by tree nut (7 cases, 30.4%), and milk (6 cases, 26.1%). Of 23 IgE-mediated food allergy patients, 6 reacted to the same trigger food of FPIES, including 2 cases to egg, 2 to cow's milk, 1 to peanut, and 1 to wheat. Of 6 cases with the same trigger to FPIES and

IgE-mediated food allergy, 2 had IgE-mediated food allergy first and developed FPIES symptoms during an OFC (one with FPIES to egg 2 years later and another to wheat 5 years later).

Resolution of FPIES

We analyzed the resolution of FPIES in 123 cases, who were followed up at least for 1 year. Thirty-three cases completely outgrew their FPIES. The median resolution age was 3 years (IQR: 1.8 – 3.5), and the median resolution time was 2.5 years (IQR: 1.1 – 4.4). The Kaplan-Meier curves of both typical and atypical FPIES cases were shown in Figure E8. The resolution rate and age were not different between typical and atypical FPIES groups ($P = .35$, the log-rank test).

Of 48 cases between 6 and 17 years of age, 10 (21%) either failed an OFC or had a convincing history of FPIES reaction in recent 1 year. In those 10 cases, fish and egg were the most common trigger foods (each $n = 3$), followed by milk, wheat, and scallop ($n = 2, 2$, and 1 respectively). One individual failed OFCs to both wheat and egg.

Discussion

It has long been speculated that more food triggers and longer duration of symptoms of FPIES would potentially impose a negative impact on patients' life.⁸ In this study, we provide direct evidence that FPIES triggered by multiple foods (≥ 3) is a risk factor for developing food aversion. Furthermore, with the addition of each individual trigger to patients affected by FPIES, the risk of developing food aversion increased by 1.65 times. This association is similar to the previous findings that children with multiple IgE-mediated food allergies have an increased risk of developing food refusal and aversion.¹²

FPIES to cow' milk and banana are significantly associated with poor body weight gain. FPIES to cow' milk was associated with chronic FPIES, and FPIES to banana was associated with multiple triggers. But, in multivariate analysis, FPIES patients induced by multiple triggers or chronic FPIES patients didn't reach statistical significance. Additional studies are required to clarify the mechanism of why those patients are at risk of food aversion or poor body weight gain. As recommended, the early, aggressive involvement of dieticians can help children affected by FPIES receive healthy nutrition and prevent the development of food aversion.⁸

Oat (34.5%) and rice (29.6%), surpassing cow's milk (19.2%), became the common trigger foods of FPIES in this study. Cow's milk was only predominant in

chronic FPIES patients. Unlike previous FPIES case series in the US,^{2,3} our finding was more similar to that in Australia, reporting grains as the predominant trigger.^{3,13} Our findings are further supported by data from other US-based studies. Recently, Blackman et al. in Texas Children's Hospital reported rice (53%) and oats (35%) were emerging as the leading causes of FPIES.⁵ Our unpublished data also showed, of 8 FPIES cases identified in a prospective healthy infant study, oat and rice (n = 3, respectively) were more common than cow's milk (n = 2) as the trigger.¹⁴ In this study, the high rate of solid-food induced FPIES might be biased by tertiary care referrals despite the inclusion of two community hospitals in the analysis. Since FPIES is still a rare disease, a nationwide survey might be required to figure out the leading trigger of FPIES in the United States.

As in other studies,²⁻⁵ this study demonstrated that high percentages of FPIES patients have eczema, IgE-mediated food allergy, and a family history of atopy and food allergy. Interestingly, 23.2% of FPIES patients in this cohort had a history of FPIAP, which is much higher than 0.16-1% in previous population-based studies.^{15,16} A similar finding was also noticed in a small prospective healthy infant cohort,¹⁴ in which 3 of 8 (37.5%) FPIES cases had FPIAP. Moreover, the FPIES patients in this study had a higher prevalence of family histories with IBD (9.4%) and celiac disease (7.3%) than other published data. In North American, the prevalence of IBD and

celiac disease in the general population are approximately 0.6% and 0.75%, respectively. Further studies are needed to clarify the association between FPIES and personal or family history of other gastrointestinal diseases.

In this study, of patients between 6 and 17 years of age, 20.8% still had persistent FPIES demonstrated by failing an OFC for FPIES or by having a recent convincing reaction. Fish and egg were the common triggers and were difficult to resolve. In other big case series, Ruffner et al. described that around 15% of FPIES had persistent FPIES beyond 5 years of age, including one patient with an OFC-proven FPIES reaction to soy which was persistent into adolescence.⁴ In the study published by Caubet et al., their Kaplan-Meier survival curves showed 30-40% of patients still not yet outgrew FPIES at 6 years of age.² Further studies are needed to better determine the risk factors for persistent FPIES and the ways to facilitate the resolution of FPIES.

Previous studies have noticed that FPIES-triggering foods have a clustering pattern, such as cows' milk and soy, rice and oat, grains and fruits/vegetable.^{2, 4, 13} In this study, we also demonstrate chicken and turkey had a strongly positive association while wheat and barley had a moderately positive association. Cow's milk and soy, shellfish and fish, and avocado and banana were weakly associated. The association may be associated with close taxonomic relationships.¹⁷ Further prospective studies

are needed to confirm the association between triggers.

One of the strengths of this study is the inclusion of multiple centers and community hospitals. However, the limited geographical focus and retrospective review in this study highlight the need for a prospective study with a larger cohort to validate the findings. Another limitation is 95.6% of FPIES cases were by referral and 70% of chronic FPIES cases were presumptive. Future prospective evaluation with additional oral challenges will better elucidate FPIES diagnosis, triggers and the timing of resolution.

In summary, we retrospectively identified 203 FPIES patients from EMR reviews over 27 years at 4 hospitals in the Partners HealthCare system. Three or more trigger is the risk factor for developing food aversion, and FPIES to cow's milk and banana are associated with poor body weight gain. These findings provide valuable information for clinical practice. Further studies are required to establish a better nutritional and feeding care for FPIES patients.

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Figure Legends

Figure 1. Foods causing food protein-induced enterocolitis syndrome (FPIES), expressed as a percentage of patients with FPIES reaction to the trigger food.

Figure 2. A heatmap shows the correlation between different trigger foods. Phi coefficient is expressed in a color legend, in which positive correlations are displayed in red, negative correlations are displayed in blue, and color intensity is proportional to the correlation coefficients (* $P < .05$; ** $P < .01$; *** $P < .001$).

Figure 3. Criteria and symptoms in food protein-induced enterocolitis syndrome (FPIES) patients, expressed as a percentage of FPIES patients with a given criterion/symptom. **(A)** Acute FPIES patients. **(B)** Chronic FPIES patients. (In Figure 3A, each minor criterion is from the 2017 international consensus guidelines.¹ For example, minor: repetitive stands for 2 or more episodes of repetitive vomiting after ingestion of the same trigger food. The details of each criterion were shown in Table E1. ED: emergency department.)

Table I. Characteristics of the food protein-induced enterocolitis syndrome patients

Characteristics	Case Number	Percentage
Total	203	
Gender, male	107	52.7%
Race		
White	174	85.7%
Black	4	2.0%
Asian	5	2.5%
Hispanic	5	2.5%
Others or unrecorded	15	7.4%
Birth and breastfeeding		
Delivery mode, C-section	53	26.1%
Prematurity	6	3.0%
Perinatal antibiotics	18	8.9%
Breastfeeding ever	152	74.9%
Personal history		
Allergic proctocolitis	47	23.2%
Gastroesophageal reflux	73	36.0%
IgE-mediated food allergy	23	11.3%
Eczema	82	40.4%
Asthma	27	13.3%
Hay fever/allergic rhinitis	29	14.3%
Family history		
FPIES	3	1.5%
Food allergy	63	31.0%
Other atopic diseases	94	46.3%
Gastroesophageal reflux	34	16.7%
Inflammatory bowel diseases	19	9.4%
Celiac disease	15	7.3%
Eosinophilic esophagitis	1	0.5%

Table II. Risk factor analysis of FPIES cases with food aversion and poor body weight gain (excluding the adult-onset FPIES cases)

Characteristics	Food aversion cases (n = 44)	No food aversion cases (n = 141)	P-value	Poor body weight gain (n = 19)	Normal body weight gain (n = 167)	P-value
Type						
Acute FPIES	41 (95.3%)	135 (95.7%)	.91	18 (94.7%)	160 (95.8%)	.82
Chronic FPIES	6 (14.0%)	16 (11.3%)	.63	6 (31.6%)	17 (10.2%)	.008
Triggers						
Cow's milk	12 (27.3%)	27 (19.1%)	.25	8 (42.1%)	31 (18.6%)	.02
Banana	5 (11.4%)	9 (6.4%)	.28	5 (26.3%)	9 (5.4%)	.001
Wheat	6 (13.6%)	3 (2.1%)	.002	2 (10.5%)	7 (4.2%)	.23
Multiple (≥ 3)	16 (36.4%)	20 (14.2%)	.001	8 (42.1%)	28 (16.8%)	.008
Demographic data						
Onset age (mo): Median (IQR) [†]	5.8 (4.0 – 7.8)	6.0 (4.9 – 8.3)	.46	6.0 (4.0 – 6.8)	6.0 (4.5 – 8.0)	.73
Gender, male	25 (58.1%)	78 (55.3%)	.75	12 (63.2%)	93 (55.7%)	.53
Race, white	36 (83.7%)	120 (85.1%)	.82	17 (89.5%)	141 (84.4%)	.56
Delivery mode, C-section	15 (34.9%)	37 (26.2%)	.27	5 (26.3%)	48 (28.7%)	.83
Prematurity	2 (4.5%)	4 (2.8%)	.58	1 (5.3%)	5 (3.0%)	.59
Perinatal antibiotics	4 (9.3%)	14 (9.9%)	.91	4 (21.1%)	14 (8.4%)	.08
Breastfeeding ever	37 (86.0%)	114 (80.9%)	.44	17 (89.5%)	135 (80.8%)	.35
Personal history						
Allergic proctocolitis	14 (31.8%)	32 (22.7%)	.22	5 (26.3%)	42 (25.1%)	.91
Gastroesophageal reflux	21 (47.7%)	47 (33.3%)	.09	9 (47.4%)	60 (35.9%)	.33
IgE-mediated food allergy	3 (6.8%)	19 (13.5%)	.23	0 (0.0%)	22 (13.2%)	.09
Eczema	22 (50.0%)	58 (41.1%)	.30	5 (26.3%)	75 (44.9%)	.12
Asthma	5 (11.4%)	16 (11.3%)	.99	2 (10.5%)	20 (12.0%)	.85
Hay fever/allergic rhinitis	3 (6.8%)	16 (11.3%)	.39	1 (5.3%)	19 (11.4%)	.42
Family history						
Food allergy	20 (45.5%)	40 (28.4%)	.04	8 (42.1%)	52 (31.1%)	.33
Other atopic diseases	22 (50.0%)	64 (45.4%)	.59	5 (26.3%)	82 (49.1%)	.06
Gastroesophageal reflux	12 (27.3%)	22 (15.6%)	.08	4 (21.1%)	30 (18.0%)	.74
Inflammatory bowel diseases	6 (13.6%)	12 (8.5%)	.32	2 (10.5%)	16 (9.6%)	.90
Celiac disease	4 (9.1%)	11 (7.8%)	.78	1 (5.3%)	14 (8.4%)	.64
Severity						
Ever ED/Hospitalization/ICU	20 (45.5%)	59 (41.8%)	.67	9 (47.4%)	71 (42.5%)	.68

[†]P-value calculated by median test. The rest is calculated by chi-square test

FPIES: food protein-induced enterocolitis syndrome. IQR: interquartile range. IgE: immunoglobulin E

ED: emergency department. ICU: intensive care unit

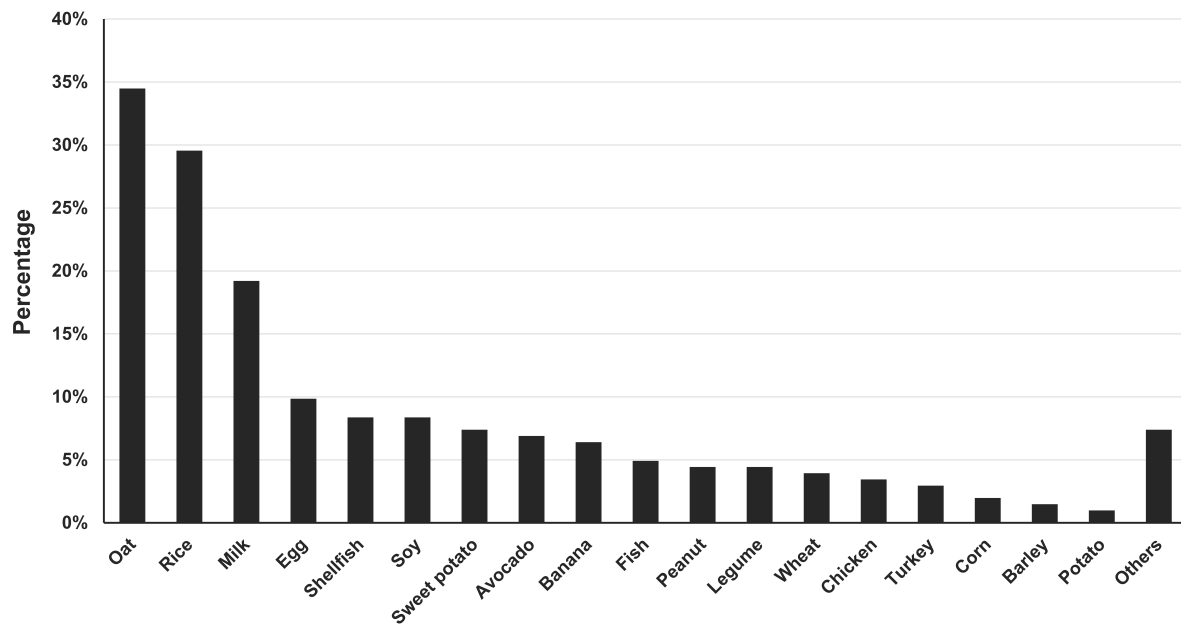
Table III. Logistic regression analysis for FPIES patients with food aversion and poor body weight gain

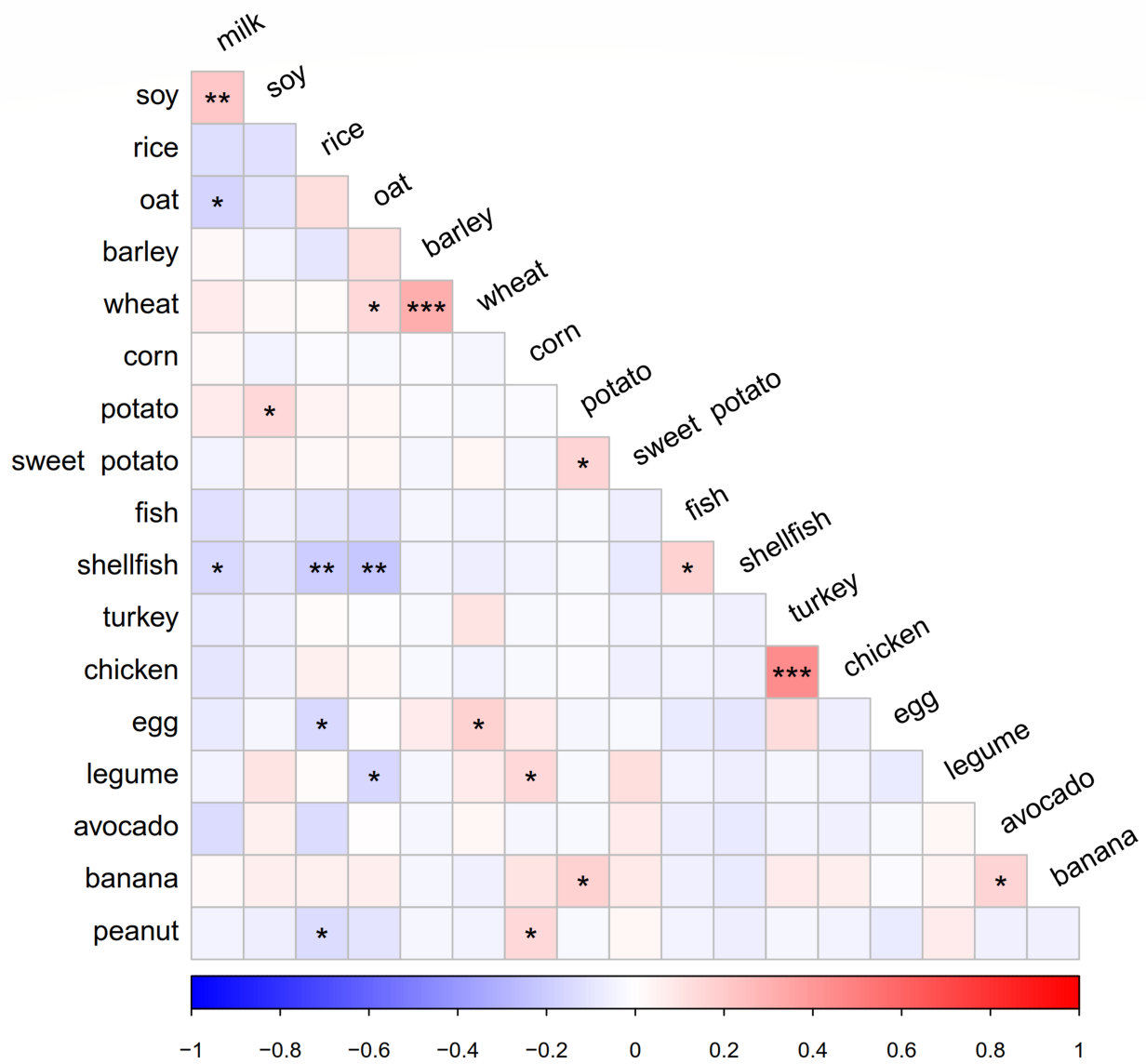
Variables	Univariate analysis		Multivariate analysis*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Food aversion				
Multiple triggers (≥ 3)	3.46 (1.59 – 7.51)	.002	3.07 (1.38 – 6.82)	.006
FPIES to wheat	7.26 (1.74 – 30.40)	.007	2.60 (0.50 – 13.56)	.26
Family history of food allergy	1.91 (0.94 – 3.90)	.08	1.79 (0.86 – 3.73)	.12
Poor body weight gain				
Multiple triggers (≥ 3)	3.61 (1.32 – 9.79)	.01	2.05 (0.63 – 6.61)	.23
FPIES to cow's milk	3.19 (1.19 – 8.59)	.02	3.41 (1.21 – 9.63)	.02
FPIES to banana	7.10 (2.05 – 24.62)	.002	7.63 (2.10 – 27.80)	.002
Chronic FPIES	4.07 (1.37 – 12.11)	.01	1.96 (0.44 – 8.83)	.38

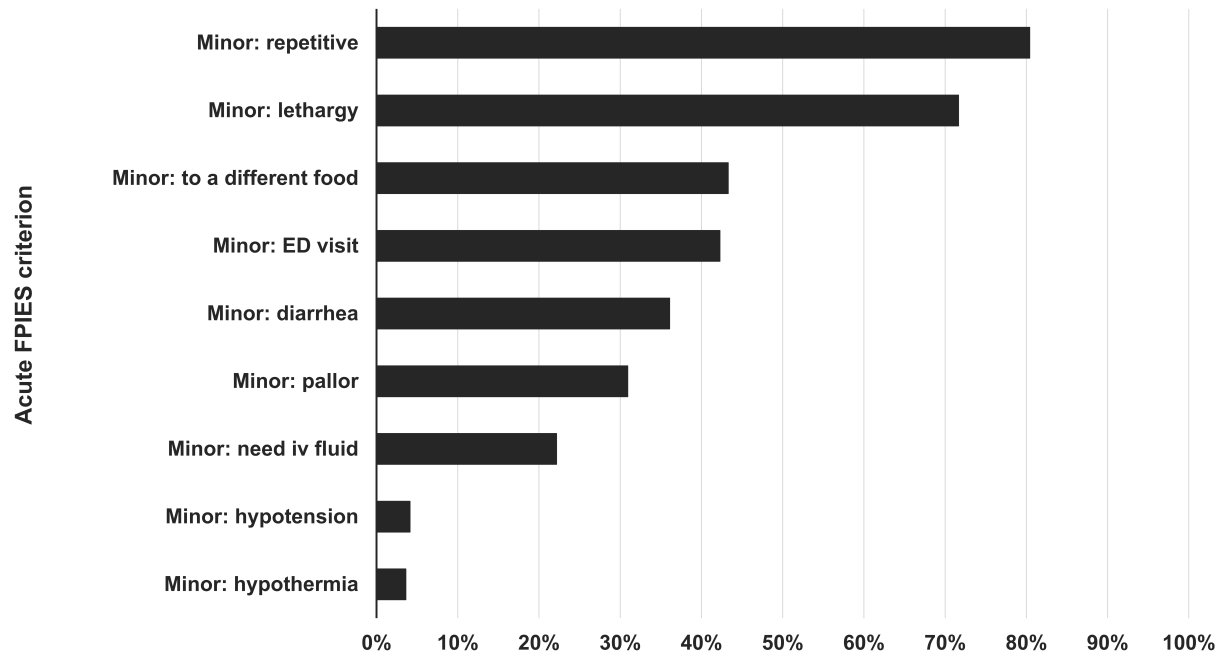
OR: odds ratio, 95% CI: 95% confidence interval, FPIES: food protein-induced enterocolitis syndrome

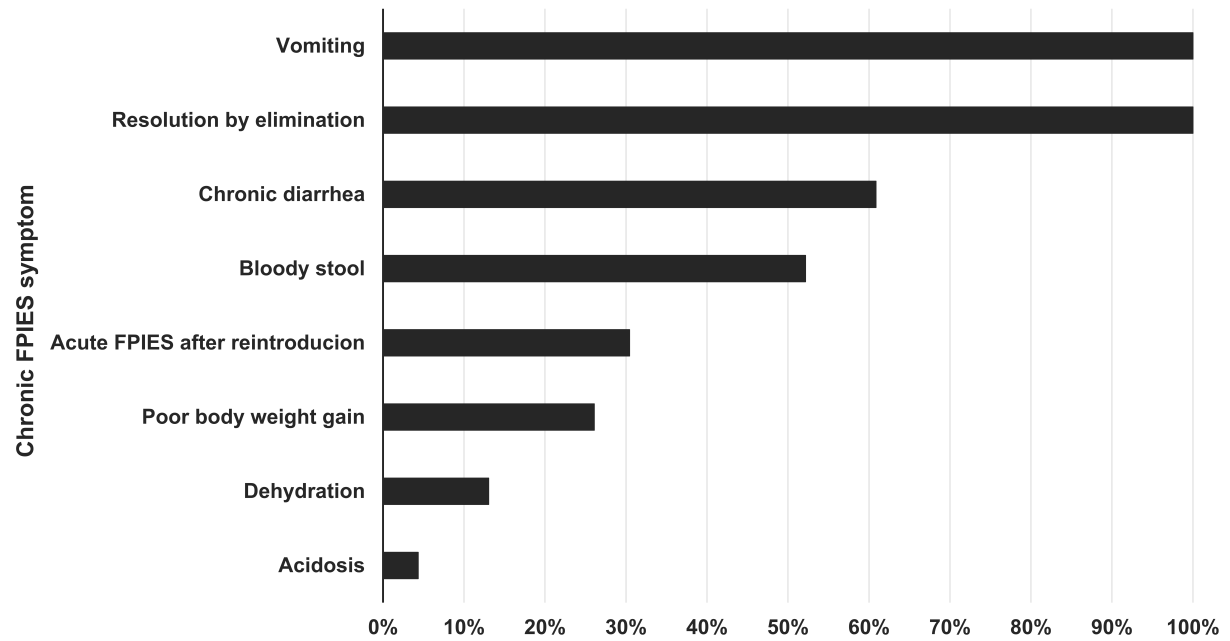
*Variables in the multivariate analysis for food aversion: gender, birth mode, prematurity, perinatal antibiotics exposure, breastfeeding, multiple trigger, FPIES to wheat, family history of food allergy.

Variables in the multivariate analysis for poor body weight gain: gender, birth mode, prematurity, perinatal antibiotics exposure, breastfeeding, multiple trigger, FPIES to cow's milk/banana, chronic FPIES.









Supplementary figure legends

Figure E1. The distribution of age of onset and diagnosis in 203 food protein-induced enterocolitis syndrome patients.

Figure E2. The distribution of age of onset and diagnosis in the adult-onset food protein-induced enterocolitis syndrome patients.

Figure E3. The distribution of age of onset and diagnosis in the food protein-induced enterocolitis syndrome patients younger than 2 years of age.

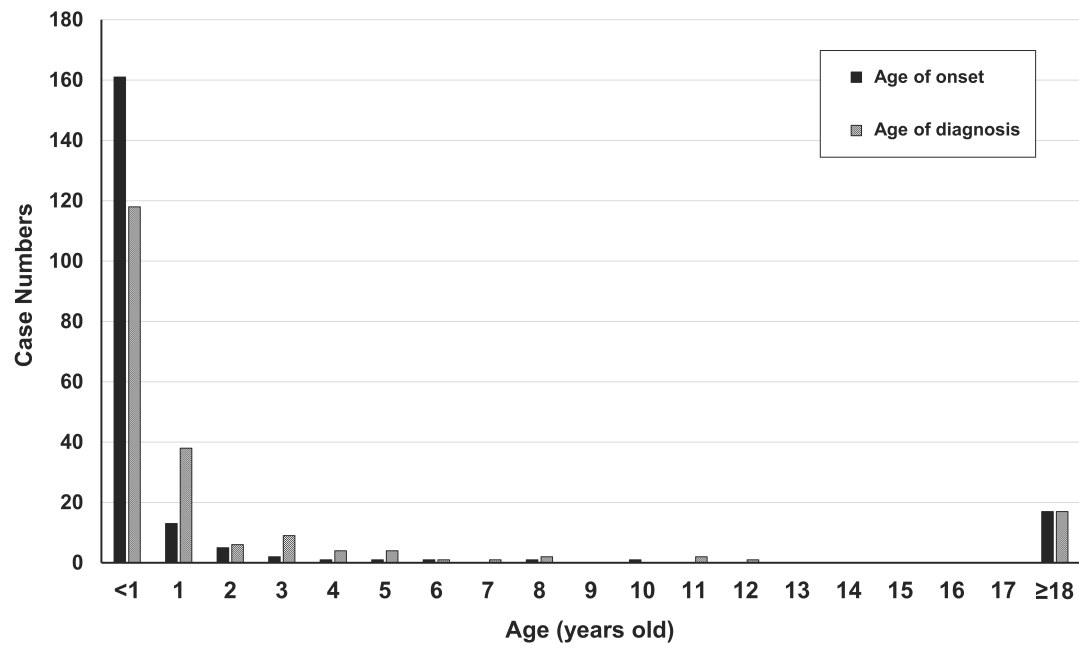
Figure E4. Foods causing acute food protein-induced enterocolitis syndrome (FPIES), expressed as a percentage of patients with FPIES reaction to the trigger food.

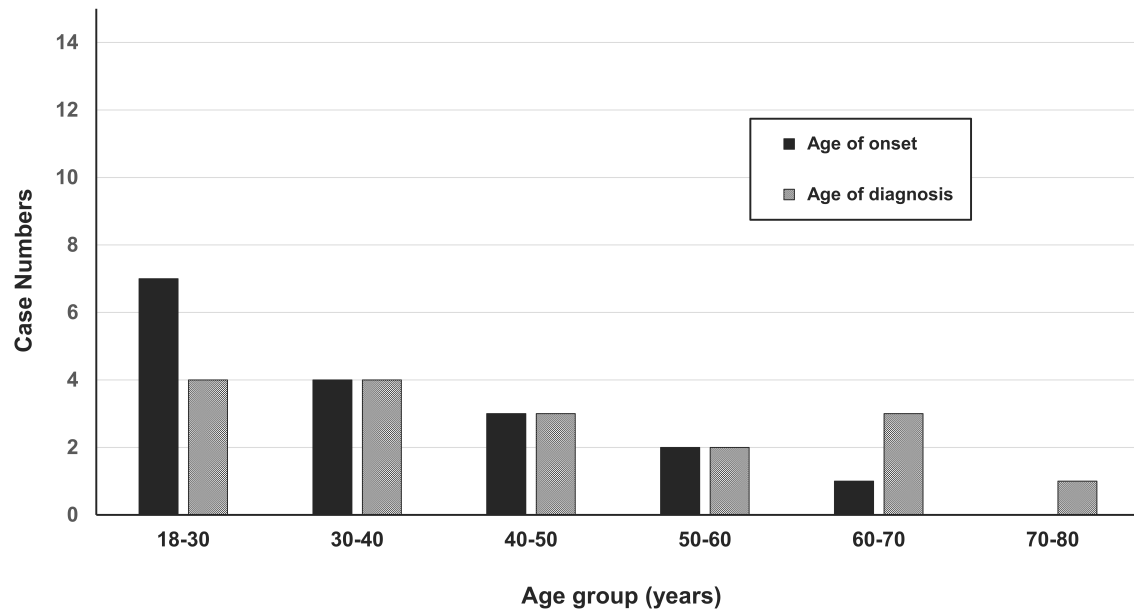
Figure E5. The distribution of the trigger food numbers causing acute and chronic food protein-induced enterocolitis syndrome.

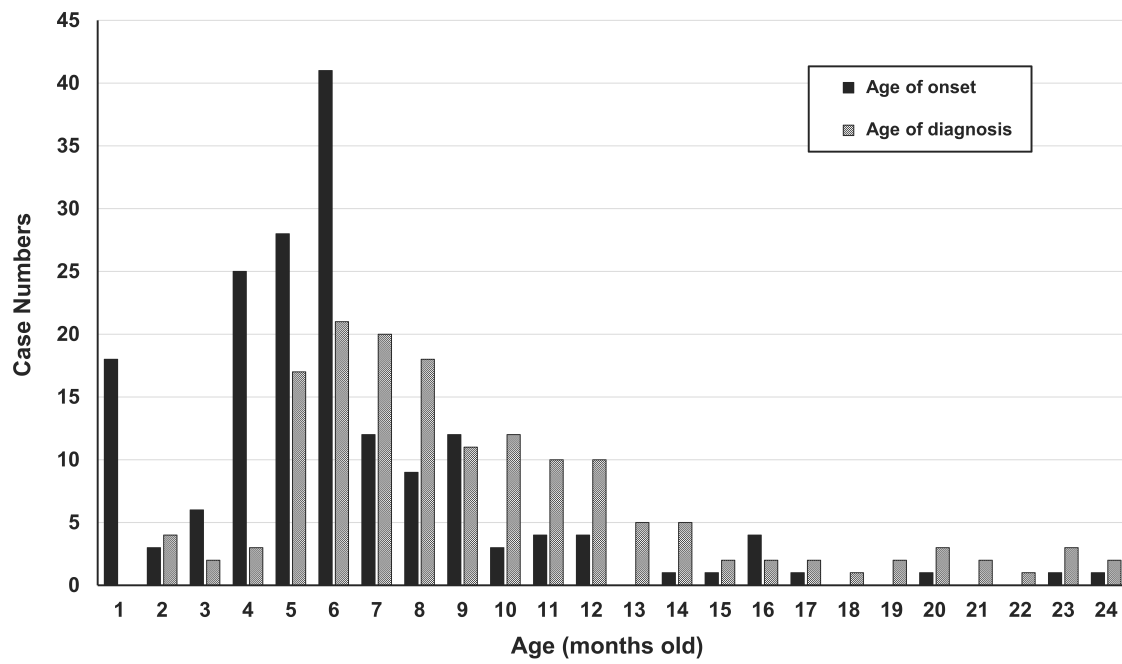
Figure E6. The comparison of the trigger foods between multiple- and oligo- food protein-induced enterocolitis syndrome (* $P < .05$; ** $P < .01$).

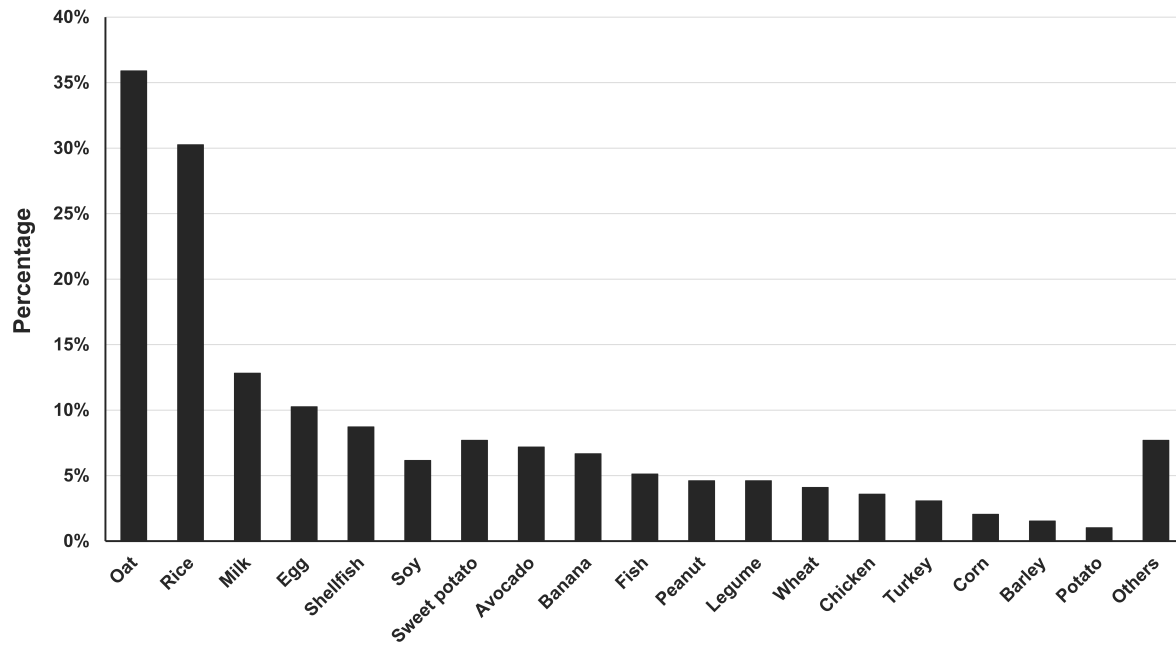
Figure E7. Criteria and symptoms in adult-onset versus non adult-onset acute food protein-induced enterocolitis syndrome (FPIES) patients, expressed as a percentage of FPIES patients with a given criterion/symptom (* $P < .05$; ** $P < .01$).

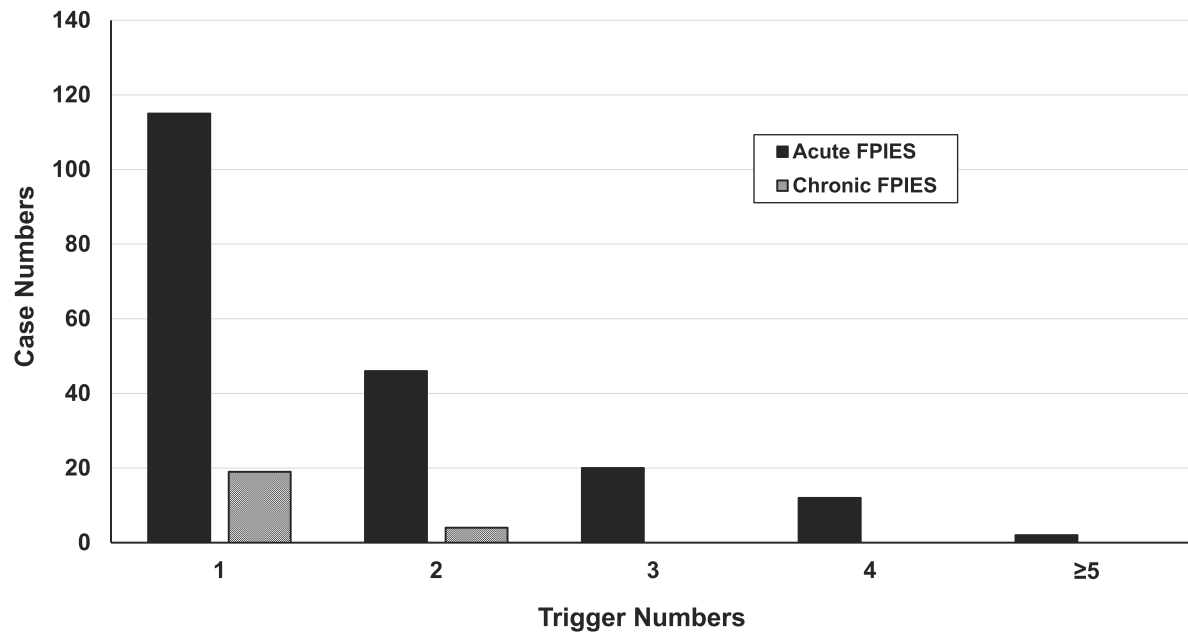
Figure E8. Kaplan-Meier survival curves for atypical and typical food protein-induced enterocolitis syndrome ($P = .35$, the log-rank test).

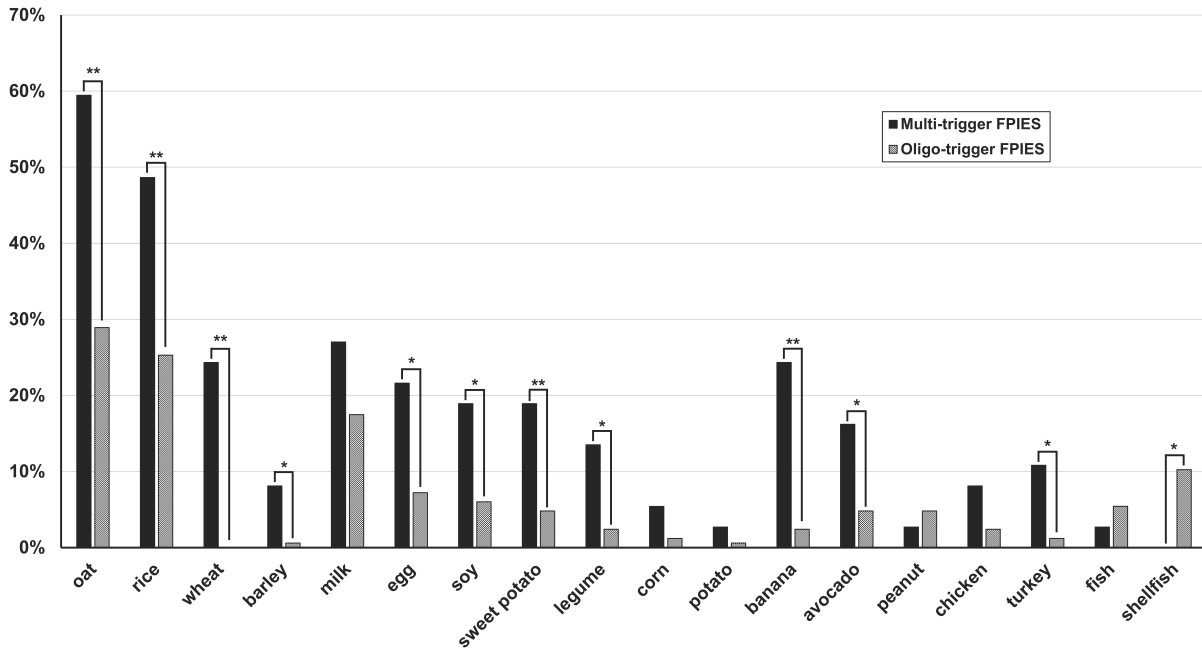


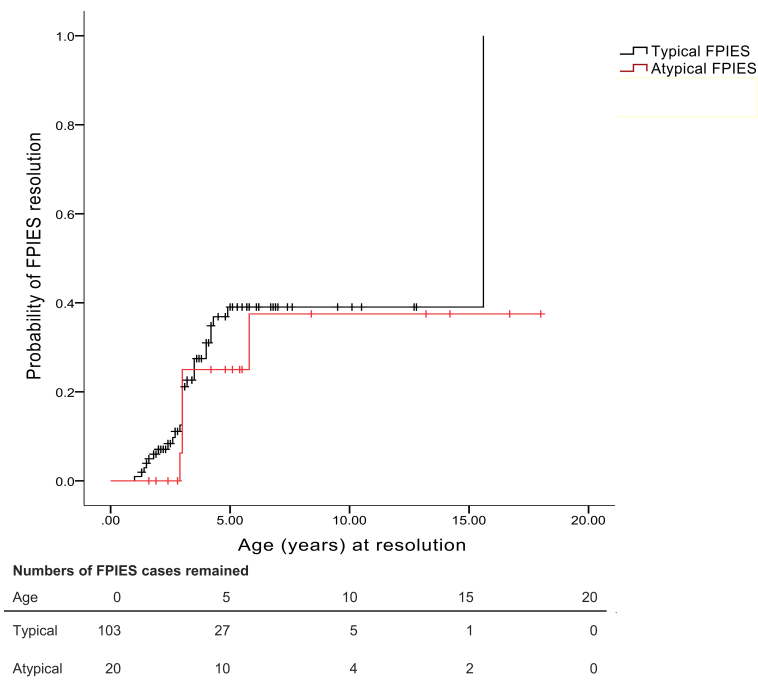












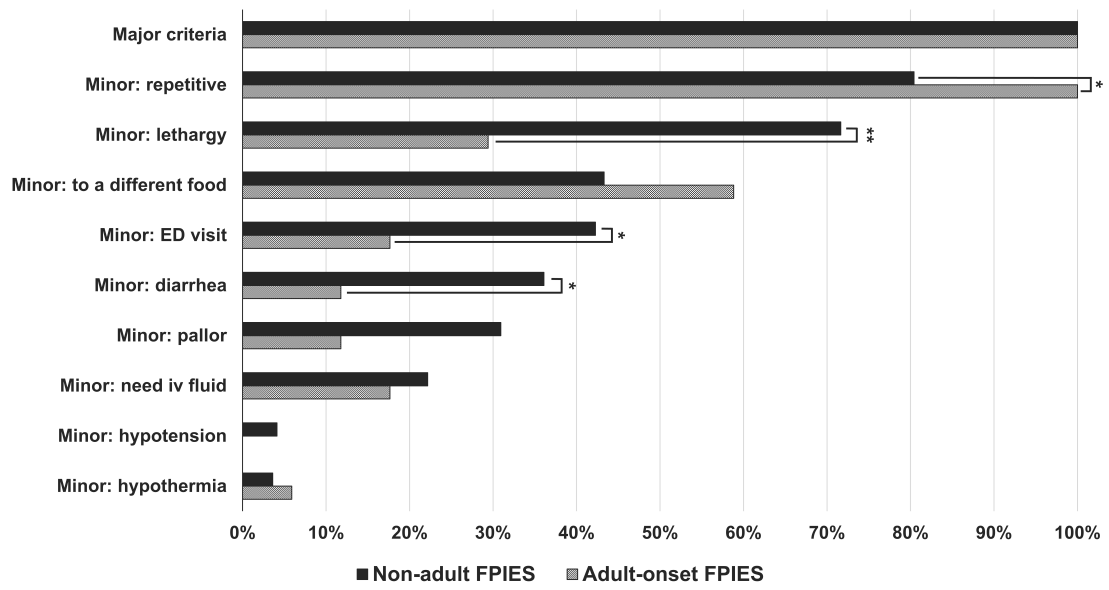


Table E1. Diagnostic criteria for patients with acute FPIES

The diagnosis of acute FPIES requires a patient meets the major criterion and 3 or more minor criteria:

Major criterion:

Vomiting 1 to 4 hours after ingestion of the trigger food without classic IgE-mediated allergic symptoms and signs.

Minor criteria:

1. Two or more episodes of repetitive vomiting after ingestion of the same trigger food.
 2. Repetitive vomiting episode happened 1 to 4 hours after ingestion of a different trigger food.
 3. Extreme lethargy during a vomiting episode.
 4. Need an emergency department visit during a vomiting episode.
 5. Need for intravenous fluid supplement during a vomiting episode.
 6. Diarrhea in 24 hours after vomiting.
 7. Hypotension documented during an episode.
 8. Hypothermia documented during an episode.
-

Adapted from the international consensus guidelines for the diagnosis and management of FPIES.¹

Table E2. Comparison of basic characteristics of multiple-trigger FPIES versus oligo-trigger

Characteristics	Multiple-trigger FPIES (≥ 3) (n = 37)	Oligo-trigger FPIES (< 3) (n = 166)	P-value
Type			
Acute FPIES	36 (97.3%)	159 (95.8%)	.67
Chronic FPIES	7 (18.9%)	16 (9.6%)	.11
Adult-onset FPIES	1 (2.7%)	16 (9.6%)	.17
Onset age (mo): Median (IQR) [†]	5.5 (4.8 – 6.5)	6.0 (5.0 – 11.0)	.04
Food aversion	16 (43.2%)	28 (16.9%)	< .001
Poor body weight gain (<3rd percentile)	8 (21.6%)	11 (6.6%)	.005
Demographic data			
Gender, male	23 (62.2%)	84 (50.6%)	.20
Race, white	33 (89.2%)	141 (84.9%)	.50
Delivery mode, C-section	9 (24.3%)	44 (26.5%)	.78
Perinatal antibiotics	6 (16.2%)	12 (7.2%)	.08
Breastfeeding ever	27 (73.0%)	125 (75.3%)	.77
Personal history			
Allergic proctocolitis	7 (18.9%)	40 (24.1%)	.50
Gastroesophageal reflux	18 (48.6%)	55 (33.1%)	.08
IgE-mediated food allergy	2 (5.4%)	25 (15.1%)	.12
Eczema	19 (51.4%)	63 (38.0%)	.13
Asthma	2 (5.4%)	25 (15.1%)	.12
Hay fever/allergic rhinitis	4 (10.8%)	25 (15.1%)	.50
Family history			
FPIES	1 (2.7%)	2 (1.2%)	.50
Food allergy	15 (40.5%)	48 (28.9%)	.17
Other atopic diseases	22 (59.5%)	72 (43.4%)	.08
Gastroesophageal reflux	8 (21.6%)	26 (15.7%)	.39
Inflammatory bowel diseases	3 (8.1%)	16 (9.6%)	.78
Celiac disease	4 (10.8%)	11 (6.6%)	.38
Eosinophilic esophagitis	0 (0.0%)	1 (0.6%)	.64
Severity			
Ever ED/Hospitalization/ICU	11 (29.7%)	72 (42.2%)	.16

[†]P-value calculated by median test. The rest is calculated by the chi-square test.

FPIES: food protein-induced enterocolitis syndrome. IQR: interquartile range. IgE: immunoglobulin E. ED: emergency department. ICU: intensive care unit