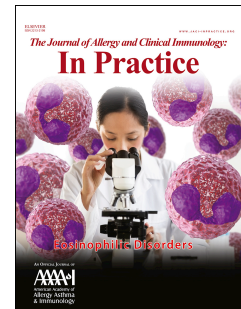


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A Slice of FPIES (food protein-induced enterocolitis syndrome): Insights from 441 children with FPIES as provided by caregivers in the International FPIES Association

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A Slice of FPIES (food protein-induced enterocolitis syndrome): Insights from 441 children with FPIES as provided by caregivers in the International FPIES Association

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Background: Food-protein induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food allergy. There is little known about demographics, food triggers and risk factors for FPIES.

Objective: We characterized demographics, food triggers, risk factors, and management in a cohort of 441 children with FPIES.

Methods: We retrospectively analyzed surveys completed by 410 caregiver-members of the International FPIES Association (I-FPIES), both at a conference for families affected by FPIES and online.

Results: The majority of children were female (50.7%), white (86.2%), and atopic (54.8%), with median age two years (range two months-19 years). The most common food groups avoided were grains (60.0%), cow's milk (52.4%), vegetables (42.7%), and fruits (38.0%). Avocado was the most commonly avoided fruit. Avoiding avocado was associated with increased likelihood of avoiding banana ($P < 0.001$). 69.4% avoided at least two food groups due to FPIES. 20.3% had a first-degree relative with FPIES. Having a first-degree relative with FPIES was associated with increased likelihood of avoiding multiple food groups ($P=0.035$).

Conclusions: Grains was the most common food group avoided, consistent with recent literature. Avocado avoidance was higher than previously reported, and this is the first report of an association between avocado and banana avoidance in FPIES. Avoiding multiple food groups due to FPIES was more common than previously reported. A large proportion of children in our cohort had first-degree relatives with FPIES and, furthermore, having a first-degree relative with FPIES was significantly associated with the affected child avoiding multiple food groups.

What is already known about this topic? FPIES is a non-IgE, cell-mediated food allergy that typically presents with delayed-onset protracted vomiting, followed by watery, sometimes bloody diarrhea. Knowledge of the condition, including trigger foods and risk factors, remains low.

What does this article add to our knowledge? Our analysis, representing 441 children with caregiver-reported FPIES, offers novel insights into the demographics of those affected, association with other atopic conditions, familial predisposition, and reported burden of dietary restriction.

How does this study impact current management guidelines? Identifying triggers and counseling affected families on dietary introduction remains challenging. Co-avoidance among foods is common. Family history of FPIES is associated with avoidance of multiple food groups. These insights may impact recommendations for food introduction.

Key Words: Food protein-induced enterocolitis syndrome, non-IgE mediated, food allergy, vomiting, diarrhea, pediatric, atopy

Abbreviations: FPIES: Food protein-induced enterocolitis syndrome, International FPIES Association (I-FPIES), IgE: immunoglobulin-E, ED: Emergency Department, OFC: oral food challenge

63 Introduction

64 Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE, cell-mediated food allergy
65 that typically presents one to four hours after ingestion of the culprit food with protracted vomiting,
66 followed by watery, sometimes bloody diarrhea. Often, the presentation of FPIES is mistaken for
67 infectious enteritis. Severe cases can be mistaken for sepsis. They manifest with lethargy, pallor,
68 hypothermia and hypotension and constitute a medical emergency as around 15% of cases result in shock.
69 Diagnosis is made by reaction history, along with clinical improvement after withdrawal of the suspected
70 trigger food.¹

71 FPIES is a rare food allergy, with incidence ranging from 0.015-0.7% in children.²⁻⁵ Given the
72 rarity of this condition, there is a paucity of epidemiological data on demographics, medical and atopic
73 comorbidities, food triggers and their prevalence, range of reactions, and risk factors for FPIES. To
74 address these knowledge gaps, the literature has called for multicenter studies evaluating this condition.⁶

75 Our objective was to characterize the demographics of children with FPIES, the range of foods
76 avoided due to FPIES, the severity and management of reactions, and risk factors for FPIES as reported
77 by a geographically-diverse population of 403 families representing 441 children.

78

79

Methods

Design

We performed a retrospective analysis of surveys completed electively by members of the International FPIES Association (I-FPIES). I-FPIES is a recognized 501(c)3 nonprofit corporation and organization that provides education, support, and advocacy for individuals with FPIES and their families, with chapters in Australia, Austria, Brazil, Egypt, Germany, Italy, United Kingdom, United States, and Qatar. Approximately 72% of 5,183 members are in the US, but the exact location of survey respondents could not be determined for this study.

The survey (available in this article's Online Repository Text) was administered to I-FPIES members both: at the FPIES Education Conference for families of children with FPIES (N= 42 respondents out of 95 distributed surveys, response rate 44.2%), held August 4, 2018 in Philadelphia, Pennsylvania, and available electronically on the I-FPIES website and on the organization's Facebook page to followers of I-FPIES between December 3, 2018 and January 7, 2019 (N=368 respondents) (**Figure I**). Families self-identified as having a child with FPIES. To ensure that the children represented were not counted twice in the analysis, surveys completed at the conference by multiple caregivers within the same family were marked. Subjects completing surveys online were instructed to complete one survey per family. The data collected were part of a survey designed to evaluate the psychosocial impact of FPIES on a child's caregiver.

Demographics of caregivers completing the survey were obtained, including age, sex, race, marital status, household income, education level, and atopic and other medical comorbidities. Demographic data for all children in the family with FPIES, including age, sex, race, and school/daycare attendance, were also obtained. Families were asked to self-report which foods were being avoided due to FPIES. Foods were divided into 13 "groups." Groups were defined as: cow's milk, soy, egg, peanut, tree nuts, fishes, shellfishes, poultries, meats, grains, vegetables, fruits and other. For categories of tree nuts,

fishes, shellfishes, poultries, meats, grains, vegetables, fruits and other, respondents were asked to specify which individual foods were avoided.

History of atopy in the child affected by FPIES and his or her caregiver, including a history of IgE-mediated food allergy, atopic dermatitis (also described as “eczema” on the survey), allergic rhinoconjunctivitis (also described as “hayfever,” “seasonal allergies” on the survey) or asthma, was assessed. For analysis of family history of atopy and its contribution to the number of foods avoided, one parent per family was considered (N=390). Caregivers were instructed to report the symptoms and management of their child’s worst FPIES reaction. Reporting of vital signs including hypotension and hypothermia during worst acute FPIES reaction was based on caregiver recollection. We did not have access to the child’s medical records. If multiple children with the same caregiver had FPIES, the caregiver was instructed to describe the worst reaction of any child.

Statistical Analysis

If multiple caregivers from the same family completed the survey, the caregiver’s report that was most complete was used for analysis of questions pertaining to the children. Not all survey respondents answered every question, thus denominators for questions were different. Descriptive statistics were used for analysis. Continuous data were described as median and range. If the caregiver completed the survey for a child who had recently outgrown FPIES, the age at which FPIES was outgrown was used for analysis. Risk factors associated with not attending school/daycare were evaluated by two-sample t-test (for child’s age) and Pearson’s Chi-squared (for written FPIES Emergency Plan and avoidance of multiple food groups). Pearson’s Chi-squared was performed to evaluate risk factors associated with avoidance of multiple food groups. A P-value <0.05 was considered statistically significant. The Boston Children’s Hospital Institutional Review Board approved this study.

127 Results

128 Demographics

129 Demographic data (**Table I**) was provided by 410 caregivers, 405 of which were parents, from
130 403 families, representing 441 children with FPIES. The majority of survey respondents were the child's
131 mother (96.1%, N=392/408), white (94.5%, N=382/404), married (92.5%, N=370/400), and highly
132 educated with a college degree or higher (83.2%, N=338/406). The median age of the affected children
133 was 2 years, with interquartile range 1.25 to 4 years. The majority of children were white (86.2%,
134 N=232/269).

135 Nearly half of families (46.4%, N=187/403) reported their child/children with FPIES did not
136 attend school or daycare, and of those not attending, more than half (53.8%, N=99/184), did not attend
137 due to concern for FPIES. Avoiding multiple food groups due to FPIES was significantly associated with
138 increased likelihood of not attending school/daycare due to FPIES (P=0.001). The majority of families
139 (73.2%, N=295/403) reported their families had been issued written FPIES Emergency Plans. Child age
140 and having been issued a written FPIES Emergency Plan were not associated with keeping children out of
141 school/daycare due to concern for FPIES (P=0.751 and 0.286, respectively). Only six children $\geq$ five
142 years of age were not in school, and only two were not in school due to FPIES.

143 Medical comorbidities of the children and their parents were self-reported and are described in
144 **Table II**. Our cohort was atopic, with 54.8% (N=221/403) of children and 47.4% (N=192/405) of parents
145 reporting a history of atopy. Comorbid IgE-mediated food allergy was reported in 25.6% (N=103/403) of
146 children with FPIES. In our cohort, 2.5% (N=10/405) of parents described a personal history of FPIES.
147 All affected parents were mothers. Having more than one child with FPIES was reported by 8.9%
148 (N=36/403) of families. Altogether, 20.3% of children (N=89/438) had a first-degree relative with FPIES.

149

150 Foods avoided due to FPIES

All 441 children had data available for foods avoided due to FPIES (**Table III**). Cow's milk was the most commonly avoided food, avoided in 52.6% (N=232/441) children. Grains was the most commonly avoided food group, avoided in 60.5% (N=267/441) children. Other commonly avoided food groups included vegetables (43.1%, N=190/441), fruits (38.3%, N=169/441), soy (37.2%, N=164/441) and egg (23.4%, N=103/441) (**Table III and Figure IIA**).

We next sought to identify specific foods avoided within food groups (**Figure IIB-D**). Oat, rice, and wheat were the most common grains avoided (**Figure IIB**). Avocado, banana, and apple were the most common fruits avoided (**Figure IIC**). Avoiding avocado was associated with increased likelihood of avoiding banana ($P < 0.001$) with 42.1% (N=24/57) of children avoiding avocado also avoiding banana. Sweet potato, peas, and corn were the most common vegetables avoided (**Figure IID**). Beef, chicken, and pork were the most common meats and poultries avoided (**Figure IIE**).

The median number of food groups avoided was three (range one to 13) (**Figure III**). Only 30.6% (N=135/441) of our cohort reported FPIES to a single food group; the majority avoided multiple food groups due to FPIES. There was no correlation between age of the child and the number of food groups avoided ($p=0.268$). Having a first-degree relative with FPIES was significantly associated with avoiding multiple food groups due to FPIES ($P=0.035$). There was no significant association between avoiding multiple foods due to FPIES and child's gender, race, or atopy or celiac disease in the child or parent (**Table IV**).

Clinical presentation and management

Four hundred and ten caregivers reported the history of their child's worst acute FPIES reaction and its management (**Table V**). Vomiting was the most commonly reported reaction with 94.3% (N=380/403) reporting vomiting within one to four hours of the culprit food's ingestion. Lethargy, pallor, decreased activity level, and diarrhea were also commonly reported. In the child's most severe acute

reaction, one-third of caregivers (33.3%, N=134/403) reported their child was “hypotensive (low blood pressure)” and 31.2% (N=128/403), reported their child was “hypothermic (low body temperature).” It was not possible to determine whether a child had history of chronic in addition to acute FPIES.

Acute FPIES is classified as “severe” by meeting required criteria: 1) projectile, repetitive (>4 episodes) emesis, 2) altered behavior (ranging from decreased activity to lethargy) 3) pallor, 4) dehydration, and 5) requirement of intravenous hydration.¹ Almost half of the caregivers, 42.4% (N=170/403), had a child who met criteria for severe FPIES during their reported most severe reaction.

The child’s worst acute FPIES reaction required a high degree of healthcare utilization: 56% (N=220/393) were evaluated in the hospital: 35.1% (N=138/393) were managed solely in the Emergency Department (ED), and 20.9% (N=82/393) were admitted. The most commonly administered pharmacotherapies were ondansetron (39.9%, N=165/403) and intravenous hydration (35.5%, 147/403). A minority of children were managed with corticosteroids (15.6%, N=63/403). In many cases, the children required multiple medications: 23.5% (N=95/403) received intravenous hydration and ondansetron, 7.4% (N=30/403) received intravenous hydration, ondansetron and intravenous or oral steroids.

One caregiver reported her child required endotracheal intubation due to the severity of the reaction. This child had underlying asthma, but no additional clinical information on the reason for intubation during the FPIES reaction was available.

Discussion

Through our analysis representing 441 children with FPIES, one of the largest cohorts in the literature, we characterized the demographics, foods avoided, spectrum of reactions and variety of medical management provided through the lens of the caregiver. A smaller retrospective chart review of 262 cases of FPIES was published in 2013 and based on the findings of a single-center in the US.⁷ A population-based study out of Australia reported on 230 children with FPIES over the years 2012-2014.⁴ Our analysis offers novel insights regarding the demographics of those affected, association with other atopic conditions, familial predisposition to FPIES, as well as the burden of foods avoided.

Features of atopy were commonly reported: 54.8% of the children had a personal history of atopy, and 47.4% of parents reported having at least one atopic condition. This is a higher percentage of atopic comorbidities than reported in prior studies.^{9, 10, 12 11} In our cohort, 25.6% of the children reported comorbid IgE-mediated food allergy, while earlier studies offer a range of 2-12%.^{9, 10, 13 11} We did not have access to records to determine whether IgE-mediated food allergy was based on positive testing alone or clinical reactions. It is possible that the increased rates of atopy and IgE-mediated food allergies could be due to differences between study populations, voluntary response bias, caregiver over-reporting, or attributable to the development of IgE-mediated allergies due to avoidance of numerous foods initially because of non-IgE-mediated reactions.

Consistent with prior literature, cow's milk was the most commonly avoided food due to FPIES.^{7, 9, 10, 13} Grains were the most commonly avoided food group. Oat was the most commonly avoided, followed by rice. Other literature has cited rice as the most common cause of solid food FPIES, rather than oat.^{4, 11} Prior studies have shown that those with FPIES to one grain have a 50% chance of developing FPIES to other grains,^{14, 15} and in our cohort, 60% of respondents who specified which grains their child avoided reported avoiding more than one grain. Wheat FPIES has not been reported in infants with oat or rice FPIES in previous studies, which is meant to reassure practitioners when advising

families on food introduction.^{10, 14} However, in our cohort, many who avoided both rice and oat also avoided wheat (48.2%, 56/116). It is not known how many children reacted to wheat versus empirically avoided it after reacting to other grains. Further study, including oral food challenges (OFCs) for children avoiding wheat without a clear reaction history, could be helpful in elucidating if wheat is responsible for FPIES reactions or is unnecessarily avoided out of parental concern given reaction to other grains.

Vegetables followed as the next most commonly avoided food group; 43.5% of our cohort avoided at least one vegetable due to FPIES. Sweet potato, peas, squash, and beans were commonly avoided.

Banana, apple, and pear were the fruits most commonly avoided by our cohort, consistent with prior literature.^{1, 11} Surprisingly, avocado, proposed to be a “lower-risk” food by the International Consensus Guidelines,¹ was the most common fruit avoided due to FPIES in our cohort. Avocado has only recently been described as an important FPIES trigger.^{11, 16} We found that a significant percentage of those avoiding avocado also avoided banana ($P < 0.001$). Interestingly, avocado and banana are both implicated in the “latex-fruit” syndrome. Further investigation is needed to determine the mechanism underlying the association between these two fruits in FPIES and whether similar antigens may play a role in FPIES.¹⁷

Blueberries and strawberries were avoided due to FPIES by numerous respondents, and are proposed as “lower-risk” foods.¹ Interestingly, coconut was also the fourth most commonly avoided fruit (after avocado, banana and apple). No prior reports of FPIES to coconut have been published to our knowledge. Additionally, to our understanding, this is the first report in the literature of nectarine, honeydew and cherry being avoided due to FPIES. While it is possible that some of these foods represent emerging triggers of FPIES, it is also possible that concern for FPIES in a highly aware caregiver may be associated with over-avoidance of certain foods that are not actual triggers of FPIES.

Interestingly, having a family history of FPIES is only recently reported in the literature.⁴ In our cohort, 8.9% of the families reported having more than one child with FPIES, 2.5% of parents reported a personal history of FPIES. In all cases, the affected parent was a mother. Data from a recent cross-sectional, population-based survey in the US of 261 children with FPIES reported that 4.9% of the families affected had multiple children with FPIES and 1.9% of affected children had a parent with FPIES; interestingly, in that report, all of the affected parents were fathers.²

In our cohort, 20.3% of children had a first-degree relative with FPIES. Children with a first-degree relative with FPIES were more likely to avoid multiple food groups than those without an affected family member ($P=0.035$). It is possible that there could be a genetic predisposition to FPIES, including multiple-food FPIES. It is also conceivable that families with a diagnosis of FPIES in another family member and their healthcare providers may have an increased awareness of the condition, leading to increased accurate diagnosis of FPIES when symptoms might have otherwise been misclassified. However, having a family member with FPIES might also lead to increased caregiver vigilance where signs and symptoms are incorrectly attributed to FPIES, or specific foods are unnecessarily avoided out of concern rather than from a reaction.

Our analysis provides rich data regarding a caregiver's description of their child's acute FPIES reaction. Acute FPIES can be a medical emergency and often requires hospitalization.¹ A large percentage of caregivers recall their children being extremely ill during their most severe acute reaction, with 42.3% of caregivers reporting symptoms that meet criteria for severe FPIES.¹ Nearly one-third of caregivers (32.9%) recalled that their child was hypotensive and a similar proportion (31.2%), recalled their child was hypothermic during his or her worst reaction. In contrast, prior literature reports that approximately 15% of patients can develop hypovolemic shock in an acute FPIES reaction.¹ As families were asked to report on any of their children's *worst* reaction, these high rates may overrepresent severe reactions among all FPIES cases. However, our cohort consists of members of I-FPIES, which is a support and advocacy group for those with FPIES. These children may have indeed had more severe reactions,

prompting caregiver involvement in the group. If caregivers recall their child being extremely ill during an acute FPIES reaction, this may potentiate unnecessary food avoidance and social restriction due to FPIES.

While previous studies describe that up to 65-80% of children have FPIES to a single food,^{7,9} 69.7% of caregivers in this cohort reported that their children avoided at least two food groups due to FPIES. As described above, many in this cohort have a family history of FPIES, which was associated with avoiding more than one food group. Additionally, the caregivers in this cohort recall their child's acute reaction as exceptionally severe. These features likely augment anxiety surrounding the condition and may cause families to restrict more foods than are necessary. Whether the food is avoided due to medical necessity, or out of precaution on the part of the caregiver, avoidance of multiple food groups impresses significant burden on families. There was a significant association between keeping the child out of school/daycare due to FPIES and caregiver perception that multiple food groups needed to be avoided ($P=0.001$). When a caregiver believes that a child must avoid multiple food groups, this may place significant stress on families by impacting their childcare and school choices. Completing an OFC to foods that are avoided, but not directly implicated in an FPIES reaction may be integral in broadening the diets of these children and improving quality of life for the entire family. Further research is needed to evaluate the psychosocial impact on FPIES on children and families. Additionally, this highlights a need to provide educational resources for children, families, childcare providers and school personnel on managing FPIES in childcare and school settings.

Our report has several limitations. Our cohort was primarily comprised of white, married, educated mothers, so our findings might not be generalizable to other populations. Families self-identified as having a child with FPIES and reported their own comorbidities, foods avoided and reaction histories. However, FPIES is diagnosed predominantly by caregiver-reported history, and only confirmed by OFC in cases when the history is unclear.¹ Selection bias is also a factor, as families elected to complete the surveys, either at an FPIES Education Conference or online, and thus we may have captured only the

most severe or medically complex cases. Caregiver reports are subject to recall bias as well. Although the surveys were distributed by I-FPIES, which has members from across the globe, we are unable to confirm the exact location of the respondents to determine which US states or other countries were represented. Prior literature has supported that food triggers vary based upon geography,^{4, 19} and despite having a large, potentially international cohort, we are unable to describe how food triggers vary based on location of the patients. Lastly, as caregivers provided details on “foods avoided due to FPIES,” we are unable to determine if the foods are avoided due to history of clinical reaction, or out of precaution due to personal or family preferences or history of reactions to other foods.

FPIES is difficult to diagnose, and acute FPIES reactions are often serious medical emergencies.¹ These difficulties may bias families and providers towards over-interpreting common clinical symptoms as food reactions. As a consequence, the diets of the children may be unnecessarily restricted, resulting in overestimation of the “foods avoided due to FPIES.” Given the psychological burden of this condition on families, as well as nutritional restriction, careful review of the medical history with a healthcare provider to help accurately define food allergies and attempting OFCs early, when clinically appropriate, may be helpful in “de-labeling” food allergies and improving quality of life.

Our analysis has many strengths, the first of which is the size of the cohort. Our data represents the demographics, foods avoided due to FPIES, reaction history and management of 441 children with FPIES and offers one of the largest cohorts described in the literature. The prevalence of avoiding multiple foods due to FPIES was striking, and factors associated with this were investigated. A familial association among FPIES cases was noted and was significantly associated with avoiding multiple food groups due to FPIES, which is novel. Avoidance of multiple food groups was also significantly associated with caregivers keeping their children out of school/daycare due to FPIES. Co-avoidance of banana and avocado was common. Avocado, which was previously classified as a “lower-risk” food, was the most common fruit avoided due to FPIES. These foods are often introduced in infancy, and thus, these findings may impact the timeline of solid food introduction for infants with FPIES. Furthermore, as the most

317 common triggers of FPIES differ based on geography, and acute management varies across facilities, this
318 study offers a more collective picture of the condition and its management than what may be gleaned
319 from a single-center study.

1. Nowak-Wegrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017; 139:1111-26.e4.
2. Nowak-Wegrzyn A, Warren CM, Brown-Whitehorn T, Cianferoni A, Schultz-Matney F, Gupta RS. Food protein-induced enterocolitis syndrome in the US-population-based study. *J Allergy Clin Immunol* 2019.
3. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol* 2011; 127:647-53.e1-3.
4. Mehr S, Frith K, Barnes EH, Campbell DE. Food protein-induced enterocolitis syndrome in Australia: A population-based study, 2012-2014. *J Allergy Clin Immunol* 2017; 140:1323-30.
5. Alonso SB, Ezquiaga JG, Berzal PT, Tardon SD, San Jose MM, Lopez PA, et al. Food protein-induced enterocolitis syndrome: Increased prevalence of this great unknown-results of the PREVALE study. *J Allergy Clin Immunol* 2019; 143:430-3.
6. Feuille E, Nowak-Wegrzyn A. Food Protein-Induced Enterocolitis Syndrome, Allergic Proctocolitis, and Enteropathy. *Curr Allergy Asthma Rep* 2015; 15:50.
7. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013; 1:343-9.
8. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998; 133:214-9.
9. Mehr SS, Kakakios AM, Kemp AS. Rice: a common and severe cause of food protein-induced enterocolitis syndrome. *Arch Dis Child* 2009; 94:220-3.
10. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol* 2014; 134:382-9.
11. Blackman AC, Anvari S, Davis CM, Anagnostou A. Emerging triggers of food protein-induced enterocolitis syndrome: Lessons from a pediatric cohort of 74 children in the United States. *Ann Allergy Asthma Immunol* 2019; 122:407-11.
12. Nowak-Wegrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2009; 9:371-7.
13. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy* 2012; 42:1257-65.
14. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003; 111:829-35.
15. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *J Allergy Clin Immunol* 2005; 115:149-56.
16. Cherian S, Neupert K, Varshney P. Avocado as an emerging trigger for food protein-induced enterocolitis syndrome. *Ann Allergy Asthma Immunol* 2018; 121:369-71.
17. Blanco C. Latex-fruit syndrome. *Curr Allergy Asthma Rep* 2003; 3:47-53.
18. Gonzalez-Delgado P, Caparros E, Moreno MV, Clemente F, Flores E, Velasquez L, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. *Pediatr Allergy Immunol* 2016; 27:269-75.

19. Diaz JJ, Espin B, Segarra O, Dominguez-Ortega G, Blasco-Alonso J, Cano B, et al. Food Protein-induced Enterocolitis Syndrome: Data From a Multicenter Retrospective Study in Spain. *J Pediatr Gastroenterol Nutr* 2019; 68:232-6.
20. Gonzalez-Delgado P, Caparros E, Moreno MV, Cueva B, Fernandez J. Food protein-induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood. *J Allergy Clin Immunol Pract* 2019; 7:670-2.
21. Jarvinen KM, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome (FPIES): current management strategies and review of the literature. *J Allergy Clin Immunol Pract* 2013; 1:317-22.
22. Nowak-Wegrzyn A, Jarocka-Cyrta E, Moschione Castro A. Food Protein-Induced Enterocolitis Syndrome. *J Investig Allergol Clin Immunol* 2017; 27:1-18.
23. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010; 126:S1-58.
24. Leonard SA, Pecora V, Fiocchi AG, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: a review of the new guidelines. *World Allergy Organ J* 2018; 11:4.
25. Lee E, Barnes EH, Mehr S, Campbell DE. Differentiating Acute Food Protein-Induced Enterocolitis Syndrome From Its Mimics: A Comparison of Clinical Features and Routine Laboratory Biomarkers. *J Allergy Clin Immunol Pract* 2019; 7:471-8.e3.
26. Holbrook T, Keet CA, Frischmeyer-Guerrerio PA, Wood RA. Use of ondansetron for food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2013; 132:1219-20.
27. Miceli Sopo S, Battista A, Greco M, Monaco S. Ondansetron for food protein-induced enterocolitis syndrome. *Int Arch Allergy Immunol* 2014; 164:137-9.
28. Miceli Sopo S, Bersani G, Monaco S, Cerchiara G, Lee E, Campbell D, et al. Ondansetron in acute food protein-induced enterocolitis syndrome, a retrospective case-control study. *Allergy* 2017; 72:545-51.

Figure I: Overview of respondents and children represented. Caregivers of children with FPIES (405 parents), representing 403 families completed a survey regarding their child's condition. If they had more than one child with FPIES they were asked to specify which food groups and specific foods their child/children avoided. They reported symptoms of their child's worst reaction, along with interventions required for management of their child's worst reaction. If a family had more than one affected child, the family was asked to indicate the worst reaction for any child.

Figure II: Food Groups Avoided by Children due to FPIES. A. Percentage of children (N=441) avoiding individual food groups. B-E: Individual foods avoided within a group, when specified by caregivers. B. Grains (250/267 specified which grains are avoided), C. Fruits (157/169 specified fruits avoided), D. Vegetables (175/190 respondents specified vegetables avoided), and E. Meats, Poultry and Fishes (79/112 respondents specified meats or poultry avoided). Only those foods avoided by >5% within the food group are represented. For complete listing of foods avoided, see Table III.

Figure III: Number of Food Groups with at Least One Member Avoided. Percentage of respondents (N=441 respondents) avoiding number of food groups. Foods avoided were defined as: cow's milk, soy, egg, peanut, tree nuts, fishes, shellfishes, poultry, meats, grains, vegetables, fruits and other.

Table I: Demographics of caregiver respondents and their children with FPIES

Caregiver's age, median (range) (N=410)	35 yr, (20-62 yr)	
Caregiver's relationship to child with FPIES (N=408)		
Mother	96.1%	(392)
Father	3.2%	(13)
Other	0.7%	(3)
Caregiver's race (N=404)		
White	94.5%	(382)
Hispanic	2.0%	(8)
Asian	1.7%	(7)
Native American	0.5%	(2)
Native Hawaiian, Pacific Islander	0.5%	(2)
Multi-race, non-Hispanic	0.5%	(2)
African American	0.2%	(1)
Caregiver's marital status (N=400)		
Married	92.5%	(370)
Single	4.7%	(19)
Divorced	2.2%	(9)
Separated	0.5%	(2)
Caregiver's highest education level (N=406)		
College	42.6%	(173)
Graduate degree	40.6%	(165)
Some college	12.3%	(50)
High school	4.4%	(18)
Annual household income (N=402)		
>\$100,000	54.7%	(220)
<\$100,000	45.3%	(182)
Child's age, median (IQR) (N=428)	2 yr, (1.25-4 yr)	
Number of food groups avoided, median (range) (N=441)	3, (1-13)	
Child's gender (N=274)	%	(N)
Male	49.3%	(135)
Female	50.7%	(139)
Child's race (N=269)		
White	86.2%	(232)
Other	5.2%	(14)
Hispanic	3.7%	(10)
Multi-race, non-Hispanic	2.6%	(7)
Asian	0.7%	(2)
Native American	0.7%	(2)
African American	0.4%	(1)
Native Hawaiian, Pacific Islander	0.4%	(1)
Child's/Children's School/Daycare Attendance (N=403)		
Attends	53.6%	(216)
Does Not Attend*	46.4%	(187)
Not attending due to concern for FPIES (N=184)	53.8%	(99)

**Six children ≥ 5 years of age were not in school; two of the six were not in school due to FPIES.* Not every question was answered by the caregiver and thus the total number of responses varies for each question. Numbers in parentheses indicate number responding to a given question. IQR: Interquartile range.

Table II: Medical Comorbidities of Children with FPIES and their Parents

	Children (N=403)		Parents (N=405)	
	%	(N)	%	(N)
Any atopy	54.8%	(221)	47.4%	(192)
Allergic rhinoconjunctivitis	17.9%	(72)	31.4%	(127)
Asthma	14.1%	(57)	22.2%	(90)
Atopic dermatitis	33.7%	(136)	13.8%	(56)
IgE-mediated food allergy	25.6%	(103)	10.0%	(41)
Celiac disease	1.2%	(5)	4.0%	(16)
FPIES	--	--	2.5%	(10)

Any atopy was defined as the presence of allergic rhinoconjunctivitis, asthma, atopic dermatitis or IgE-mediated food allergy.

Table III: Number of Children Avoiding a Specific Food

Food Avoided	N	Food Avoided	N
Cow's Milk	232	Fruits	169
Soy	164	Avocado	57
Egg	103	Banana	53
Peanut	54	Apple	35
Tree Nuts	37	Coconut	22
Cashew	2	Pear	19
Grains	267	Blueberry	19
Oats	164	Strawberry	12
Rice	150	Peach	11
Wheat	71	Orange	8
Barley	17	Mango	9
Quinoa	12	Watermelon	8
Rye	2	Raspberry	7
Millet	1	Grape	7
Vegetables	190	Pineapple	6
Sweet potato	73	Kiwi	5
Peas	41	Cherry	3
Corn	31	Honeydew	1
Squash	28	Nectarine	1
White potato	23	Meats	80
Pumpkin	15	Beef	39
Broccoli	12	Pork	18
Spinach	11	Lamb	11
Cauliflower	9	Bison	2
Lentil	7	Veal	1
Tomato	7	Moose	1
Chickpea	5	Shellfishes	26
Cucumber	4	Mussels	1
Pepper	3	Other	43
Parsnip	2	Oils	5
Beet	1	Food coloring/dyes	5
Garlic	1	Cocoa	3
Jicama	1	Sesame	3
Onion	1	Chocolate	2
Mushroom	1	Vanilla	1
Poultry	53	Flax	1
Chicken	30	Gelatin	1
Turkey	1	Goat's Milk	1
Duck	1	Hemp milk	1
Fishes	41	Honey	1
Salmon	5	Sunflower	1
Pollock	1		

Foods groups with at least one member avoided (in bold) and specific foods avoided due to FPIES are indicated (N=441 children). Not all respondents specified individual foods avoided.

Table IV: Factors associated with avoiding multiple foods due to FPIES

	Child			Parent		
	Single food group avoided % (N)	Multiple food groups avoided % (N)	P-value	Single food group avoided % (N)	Multiple food groups avoided % (N)	P-value
Male Child	46.7% (35/75)	48.7% (77/158)	0.768	--	--	--
White Race	83.8% (67/80)	87.2% (156/179)	0.465	--	--	--
Any atopy	50.4% (62/123)	56.9% (152/267)	0.229	41.8% (56/134)	51.7% (156/302)	0.057
Allergic rhinoconjunctivitis	15.4% (19/123)	18.7% (50/267)	0.430	26.9% (36/134)	33.8% (102/302)	0.152
Asthma	12.2% (15/123)	15.0% (40/267)	0.463	20.9% (28/134)	24.2% (73/302)	0.454
Atopic dermatitis	27.6% (34/123)	37.0% (99/267)	0.068	10.4% (14/134)	17.5% (53/302)	0.058
IgE-mediated food allergy	22.8% (28/123)	26.6% (71/267)	0.420	7.5% (10/134)	11.3% (34/302)	0.225
Celiac disease	1.6% (2/123)	1.1% (3/267)	0.682	2.2% (3/134)	4.6% (14/302)	0.233
First-degree relative with FPIES	14.2% (19/134)	23% (69/300)	0.035	--	--	--

Any atopy was defined as the presence of allergic rhinoconjunctivitis, asthma, atopic dermatitis or IgE-mediated food allergy.

Table V: Manifestations & Management of Most Severe Acute FPIES Reaction

Sign of Reaction (N=403)	%	(N)
Any vomiting within 1-4 hours of eating culprit	94.3%	(380)
1-3 episodes of emesis	21.3%	(86)
> 4 episodes of emesis	73.0%	(294)
Any diarrhea within 24 hours of eating culprit	70.0%	(282)
Non-bloody diarrhea	42.7%	(172)
Bloody diarrhea	27.3%	(110)
Lethargy	90.8%	(366)
Pale-appearing skin	85.9%	(346)
Decreased Activity Level	76.2%	(307)
Unable to tolerate liquids by mouth	48.4%	(195)
Hypotension (low blood pressure)	33.3%	(134)
Hypothermia (low body temperature)	31.8%	(128)
Location of Highest Level of Care Administered (N=393)		
Home	44.0%	(173)
Emergency Department	35.1%	(138)
Inpatient Unit	20.9%	(82)
Pharmacotherapy Administered (N=403)*		
Ondansetron	39.9%	(165)
Intravenous Hydration	35.5%	(147)
Intravenous Steroids	9.4%	(39)
Oral Steroids	5.8%	(24)

*23.5% (95 children) received both intravenous hydration and ondansetron, 7.4% (30 children) received both intravenous hydration, ondansetron and intravenous or oral steroids.

**Figure II: Food Groups
Avoided by Children due to
FPIES**

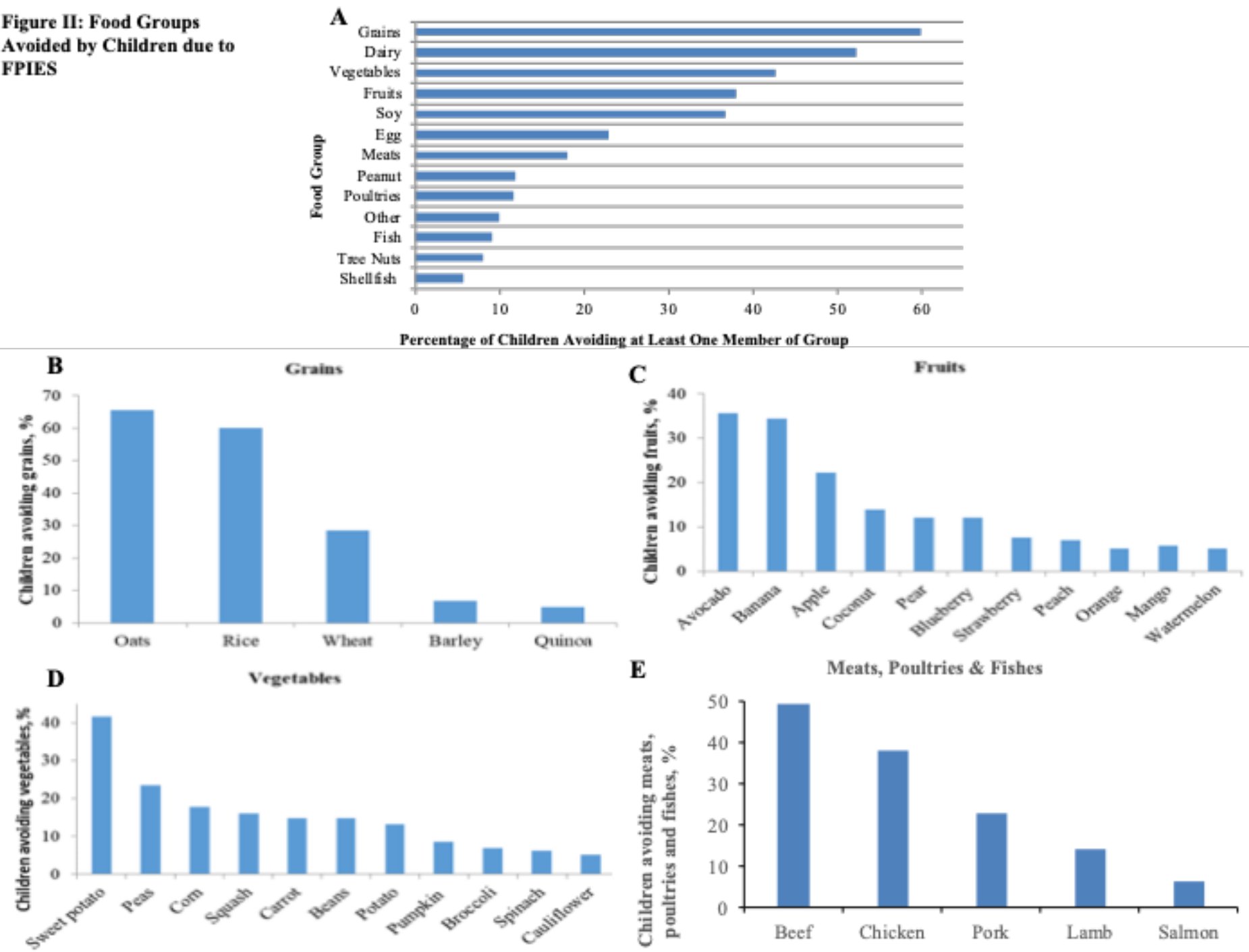


Figure III: Number of Food Groups with at Least One Member Avoided.

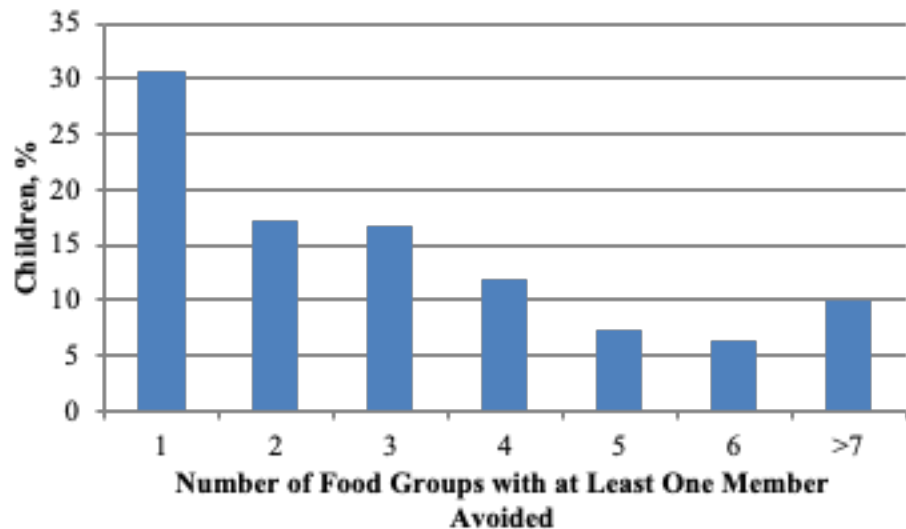


Figure 1: Overview of respondents and children represented.

