

Elevated Atopic Comorbidity in Patients with Food Protein–Induced Enterocolitis



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What is already known about this topic? Food protein–induced enterocolitis syndrome is associated with high atopic comorbidity; however, there is little data examining potential mechanisms that underlie this association.

What does this article add to our knowledge? We performed longitudinal analysis in a primary care birth cohort. Although we observe high levels of atopic comorbidity, we did not find evidence for a direct causal relationship between prior FPIES and later atopy.

How does this study impact current management guidelines? Our data suggest a possible shared predisposition to FPIES and atopy, though provider bias toward diagnosing atopic disorders in patients with FPIES may contribute to these associations. Clinicians should monitor patients with FPIES for symptoms of atopic disorders.

BACKGROUND: Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy. Its relationship to the major atopic manifestations (atopic dermatitis [AD], IgE-mediated food allergy [IgE-FA], allergic rhinitis [AR], asthma) is not understood.

OBJECTIVE: To determine the clinical characteristics, epidemiologic features, and natural history of FPIES in relation to the major atopic manifestations.

METHODS: We examined our primary care birth cohort of 158,510 pediatric patients, of whom 214 patients met 2017 FPIES diagnostic criteria. We measured the influence of FPIES on developing subsequent atopic disease.

RESULTS: Pediatric FPIES incidence was between 0.17% and 0.42% depending on birth year. As in prior reports, most patients had an acute presentation (78%), and milk, soy, oat, rice, potato, and egg were common triggers. The mean age of diagnosis was 6.8 months. Atopic comorbidity was higher in patients with FPIES compared with healthy children (AD, 20.6% vs 11.7%; IgE-FA, 23.8% vs 4.0%; asthma, 26.6% vs 18.4%; AR, 28.0% vs 16.7%; $P < .001$ χ^2). However, longitudinal analyses indicated that prior FPIES did not influence the rate of atopy development.

CONCLUSIONS: The incidence of FPIES in our cohort was initially low, but is increasing. Food allergen distribution, presentation, and age of onset are similar to prior reports. Patients with FPIES have high rates of atopic comorbidity. However, longitudinal analysis does not support direct causation as the etiology of these associations. Rather it suggests a shared predisposition to both types of allergy, or associative bias effects. This work refines our understanding of the natural history of FPIES by elucidating associations between FPIES and atopy. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:1039-46)

Key words: Food protein–induced enterocolitis syndrome; FPIES; Food hypersensitivity; IgE-mediated food allergy; Asthma; Dermatitis, atopic; Rhinitis, allergic; Epidemiology; Atopic march

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Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that manifests with gastrointestinal symptoms, and is frequently triggered by cow's milk, soy, and grains.¹⁻³ The onset of FPIES typically occurs during infancy, though there are limited reports in older children and adults.^{4,5} The symptoms of FPIES vary with the frequency of allergen exposure and are classified into acute or chronic forms.⁶ Acute FPIES occurs when allergen exposure is intermittent, and

*Abbreviations used**AD- Atopic dermatitis**AR- Allergic rhinitis**CHOP- Children's Hospital of Philadelphia**EMR- Electronic medical record**FPIES- Food protein–induced enterocolitis syndrome**ICD- International Classification of Diseases**IgE-FA- IgE-mediated food allergy*

manifests as delayed (2 to 4 hours after ingestion) vomiting with or without diarrhea, pallor, or hypotension. Because of the risk of dehydration, acute FPIES can be a medical emergency. In contrast, chronic FPIES typically occurs in young infants ingesting the allergen daily and manifests as progressive watery diarrhea, emesis, and poor weight gain.⁷

First described in the 1960s,^{8,9} it was not until 2015 that an FPIES-specific international classification of diseases code was introduced.³ Perhaps because of its relatively recent definition, the epidemiological features of FPIES are still being determined. In one study, Katz et al¹⁰ used a prospective birth cohort from a single Israeli hospital and observed a 2-year cumulative incidence of cow's milk FPIES of 0.34%. By comparison, Mehr et al¹¹ studied an Australian primary care–based cohort using a cross-sectional disease surveillance survey and found a cumulative incidence ranging from 0.013% to 0.024%. Large North American retrospective case series of patients with FPIES have estimated the point prevalence at approximately 1%.^{1,12} Despite these well-designed studies, the true incidence of FPIES remains largely unknown.

In contrast to FPIES, our knowledge surrounding the epidemiologic features of the atopic manifestations (atopic dermatitis [AD], IgE-mediated food allergy [IgE-FA], allergic rhinitis [AR], asthma) is more robust. For example, it is now well established that the development of one atopic manifestation increases an individual's risk of developing subsequent atopic disease in a clinical progression known as the “atopic march.”¹³ However, as FPIES is a non-IgE-mediated food allergy, its pathologic connection with the classic atopic manifestations is less clear. Interestingly, patients with FPIES have consistently been reported to have increased rates of AD (6% to 51%), IgE-FA (4% to 5%), asthma (3% to 25%), and AR (13.6% to 72%) when compared with healthy children.^{14–19} Though shown across multiple studies, it is not known whether these associations represent a shared predisposition between FPIES and the atopic manifestations, if FPIES predisposes to the development of atopic disease, or if this association is the result of methodologic bias.

In this study, we use electronic medical record (EMR) review of a large primary care birth cohort to determine the natural history, clinical characteristics, and epidemiologic features of physician-diagnosed FPIES. This unique approach allows us to examine the natural incidence of FPIES over time, and in relationship to patient age. We further define children with FPIES in terms of demographics, clinical characteristics, and most common food allergens. Finally, we measure the prevalence of atopic comorbidities in patients with FPIES and perform multivariable analyses to determine if prior FPIES diagnosis influences the rate of atopy development. This work refines our view of the natural

history of FPIES and expands our understanding of the relationship between this condition and atopic disease.

METHODS**Birth cohort generation and clinical data extraction**

The Children's Hospital of Philadelphia (CHOP) network consists of 31 outpatient clinical care sites across the greater Delaware valley that provide both primary and subspecialty pediatric care. Data from this network have previously been validated as a tool to assess regional disease epidemiology.^{20,21}

To determine the epidemiologic relationships between FPIES and the atopic disorders, we examined the EMRs (Epic Systems Inc., Verona, Wis) of the 158,510 children who are part of the CHOP primary care birth cohort, as previously defined.²¹ To be included in this cohort, patients were required to have established care in the CHOP primary care network before their first birthday, and between January 1, 2001, and December 31, 2018. Patients were also required to have received primary care from a CHOP-affiliated practice for at least 2 years. Observation time for children was censored on the date of their last face-to-face outpatient health care encounter in our health system before their 17th birthday, and we assumed that patients were observed continuously until they were censored.

FPIES cohort generation, definition, and validation

Patient records within the birth cohort were selected for additional review if International Classification of Diseases (ICD) codes corresponding to FPIES were used (ICD-9: Allergic gastroenteritis and colitis [diagnosis name 'Food protein-induced enterocolitis syndrome'], 558.3, and ICD-10 Food protein–induced enterocolitis syndrome, K52.2). A manual review of all charts containing FPIES ICD codes was performed by pediatric allergists. Patients were excluded if it was not possible to verify an eliciting allergen and reaction symptoms consistent with 2017 FPIES diagnostic criteria for both acute and chronic FPIES.⁶ We excluded cases of suspected chronic FPIES without historical, accidental, or physician-supervised challenge confirming the FPIES phenotype. If FPIES diagnosis was not clear from the EMR, 3 physicians jointly reviewed the patient data to make a determination. Additional features including age of onset and eliciting allergens were recorded. Only allergens documented to elicit FPIES reactions are reported.

Atopic disease cohort generation

We ascertained the presence or absence of atopic conditions of interest (AD, IgE-FA, asthma, and AR) using a combination of diagnosis codes, allergen information, and medication prescriptions as described previously.^{21,22} All diagnoses were made in accordance with established practice parameters. For inclusion in a disease cohort, patients were required to have diagnosis codes representative of an atopic condition on 2 separate care visits, occurring at least 6 months apart.

To maximize the specificity of our IgE-FA cohort, we: (1) required an epinephrine autoinjector prescription and a food allergen entry in the EMR allergy module, (2) excluded diagnosis codes relating to food protein–induced enterocolitis syndrome and eosinophilic esophagitis, and (3) recoded patients with diagnosis codes corresponding to lactose intolerance and gluten sensitivity (celiac disease) as non-milk or non-wheat allergic, respectively. In addition, a manual chart review was performed on the cohort of all patients with FPIES to confirm symptoms of IgE-mediated food

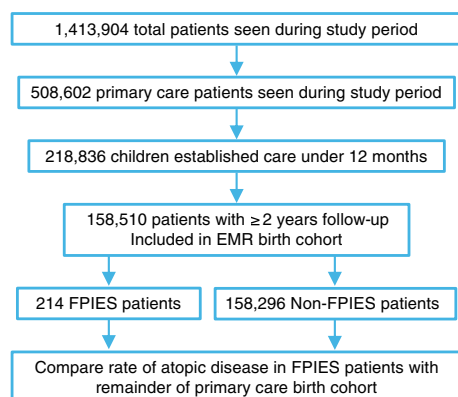


FIGURE 1. Study design. We performed a retrospective review of 158,510 patients using an EMR-based primary care birth cohort to identify patients with food protein–induced enterocolitis syndrome (FPIES) and non-FPIES patients with atopic diagnoses. To do so, we used a combination of ICD-9/10 codes, allergen and medication information, and manual chart review. *EMR*, Electronic medical record; *ICD*, International Classification of Diseases.

allergy separate from symptoms of FPIES, and to record allergens that elicited symptoms.

To maximize specificity of our asthma cohort, we: (1) limited our analysis to ICD codes occurring after 1 year of age, (2) required prescriptions for asthma-specific medications (eg, albuterol, inhaled corticosteroid) on at least 2 separate dates, and (3) ignored ICD codes related to viral-induced wheeze and reactive airway disease.

Statistics

Chi-squared testing was initially used to examine the frequency of atopic manifestations in patients with FPIES compared with those without. We studied longitudinal disease diagnosis in individuals across our birth cohort and performed case-control comparisons using Cox proportional hazards monitoring with adjustments for demographic covariates (birth year, race, ethnicity, gender, and payer type). Peak age of diagnosis was defined as the mode of the disease incidence curve. Longitudinal comparisons were performed via 2 approaches. First, we examined the rate of onset of atopic diseases in the FPIES and non-FPIES cohorts irrespective of the timing of FPIES diagnosis. Next, we examined the rate of onset of atopic diseases in patients with, or without, a preceding FPIES diagnosis. In the latter analysis, we treated children who had FPIES after the outcome of interest the same as children who did not have the exposure condition during our observation time. Because of the variable follow-up time, we chose Cox proportional hazard ratios with confidence intervals to present our results. Kaplan-Meier curves were plotted to display risk over time. After adjustment for the covariates (birth year, race, ethnicity, sex, insurance payer), *P* values less than .05 were considered significant.

Availability of data

The dataset supporting the conclusions of this article is available in the Zenodo repository (<http://10.5281/zenodo.3508812>).

Ethical and regulatory oversight

Chart review was performed with approval from the CHOP Institutional Review Board.

TABLE I. Demographic characteristics of the EMR cohorts

Characteristic	Cohort % (n) (158,510 total patients)	
	Primary care 99.86% (158,296)	FPIES 0.14% (214)
Sex, % (n)		
Male	51 (81,129)	64 (137)
Female	49 (77,167)	36 (77)
Race, % (n)		
White	50 (78,526)	77 (165)
Black	32 (50,828)	9 (19)
Asian/Pacific Islander	4 (5816)	4 (8)
Other	2 (3153)	2 (5)
Unknown	12 (19,973)	8 (17)
Ethnicity, % (n)		
Hispanic/Latino	7 (10,484)	5 (11)
Non-Hispanic/Latino	93 (147,812)	95 (203)
Birth year, % (n)		
2000 to 2004	9 (13,356)	<1 (1)
2005 to 2009	38 (60,562)	7 (14)
2010 to 2014	39 (61,970)	50 (106)
2015 or later	14 (22,408)	43 (93)
Payer type, % (n)		
Medicaid	33 (52,254)	16 (35)
Non-Medicaid	67 (106,042)	84 (179)

EMR, Electronic medical record; *FPIES*, food protein–induced enterocolitis syndrome.

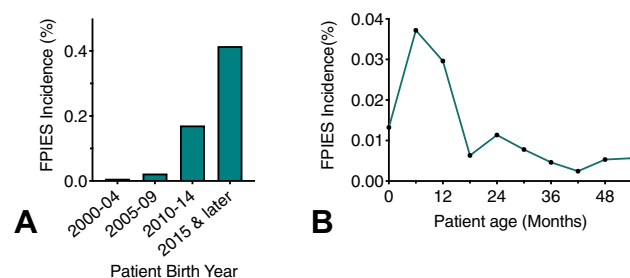


FIGURE 2. Incidence of FPIES. **A**, Incidence of FPIES by birth year. **B**, Incidence of FPIES by age. *FPIES*, Food protein–induced enterocolitis syndrome.

RESULTS

Cohort demographics

Of the 158,510 children in the CHOP primary care birth cohort, 214 patients had a confirmed diagnosis of FPIES after imposing EMR criteria and performing physician chart review (Figure 1). The demographic characteristics of the cohorts (Table I) demonstrate significant predominance of male and white race patients in the FPIES group compared with the overall cohort (64% males in FPIES vs 51% overall, 77% white in FPIES cohort vs 50% in overall; $\chi^2 P < .001$ for both). Private insurance was also more common in the FPIES cohort (84% in the FPIES cohort vs 67% in overall; $\chi^2 P < .001$).

FPIES incidence and age of diagnosis

The cumulative incidence of FPIES across all years within our birth cohort was 0.14%. However, the distribution of FPIES

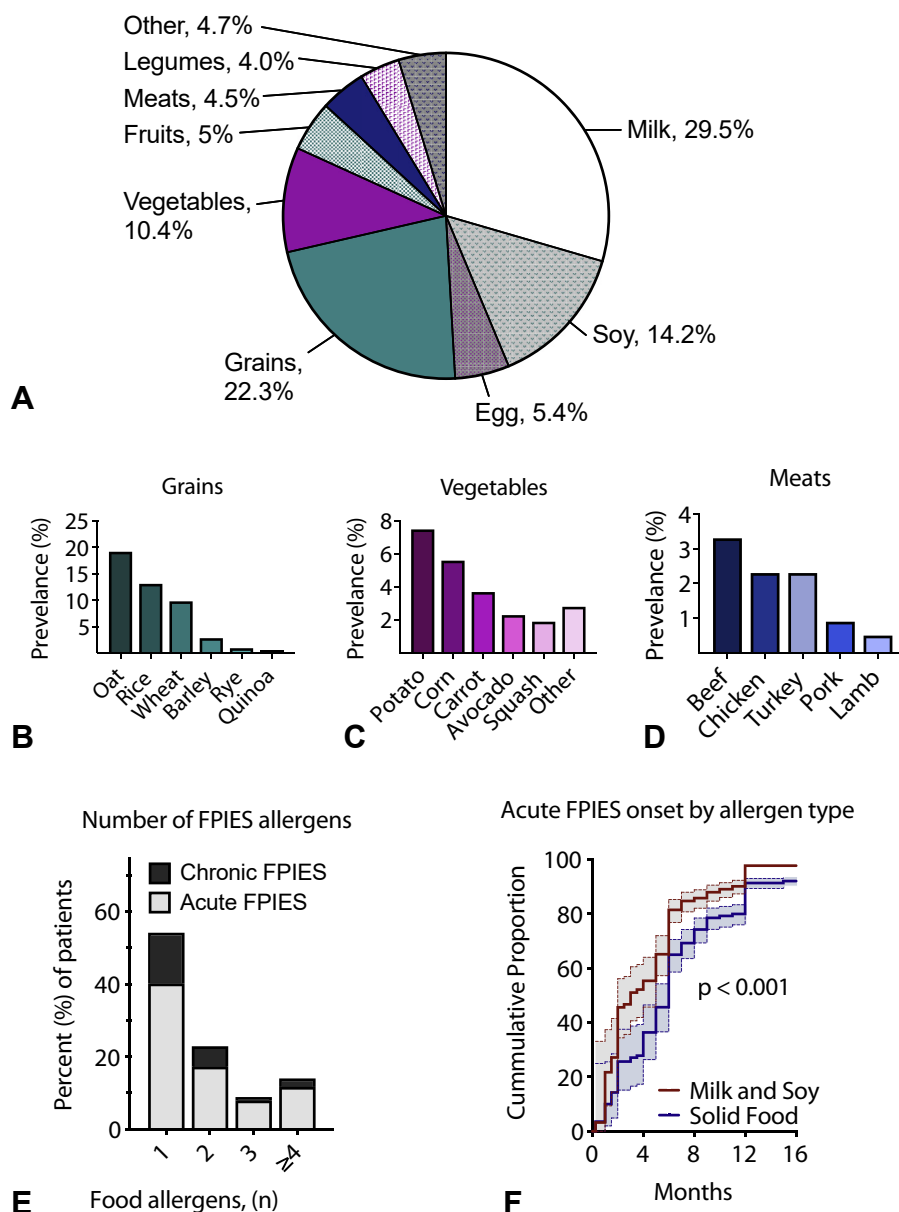


FIGURE 3. FPIES food allergens and presentation. **A**, Frequency of the most common food allergens in patients with FPIES. Frequency of FPIES allergens within categories of **(B)** grains, **(C)** vegetables, and **(D)** meats. **E**, Percent of patients presenting with acute or chronic FPIES phenotype. **F**, Onset of acute FPIES to milk and soy as compared with solid foods, in relation to patient age. *FPIES*, Food protein–induced enterocolitis syndrome.

diagnoses over time was unequal (Figure 2, A), with highest FPIES incidence in the patient subcohort born between 2015 and 2018 (maximum of 0.415%). We next examined the age-specific incidence rate for FPIES in our cohort (Figure 2, B); in order to determine how patient age affected incidence of FPIES, we examined the FPIES age-specific incidence rate. The peak age-specific FPIES incidence occurs at 6 months of age. Overall, the majority of patients in our cohort presented under 1 year of age, which is consistent with previous data on FPIES.^{1,3,17,23} However, there were a small number of children in this cohort who presented with new symptoms of FPIES beyond the age of 3. From 3 years of age to 12 years of age, the

incidence remained low (0.0041 ± 0.001 , mean $\pm$ standard deviation). There was no pattern of consistent eliciting allergens in this older FPIES group.

FPIES causal food allergens and acuity

We next examined patient data to characterize the presentation of FPIES within this cohort. Board-certified allergists reviewed the charts of patients with FPIES to determine which foods were responsible for symptomatic FPIES reactions. Consistent with previous reports, the most common causal foods were milk, grains, and soy (Figure 3, A). Milk and soy represented the most prevalent single food triggers, followed by egg,

TABLE II. Cumulative incidence of atopic comorbidity in FPIES

	Cohort %		<i>P</i> value	Odds ratio [95% CI]
	Primary care (n = 158,296)	FPIES (n = 214)		
Atopic dermatitis	11.7%	20.6%	<.001	2.0 [1.5-2.7]
IgE-food allergy	4.0%	23.8%	<.001	7.6 [5.5-10.4]
Asthma	18.4%	26.6%	<.01	1.6 [1.2-2.2]
Allergic rhinitis	16.7%	28.0%	<.001	1.9 [1.4-2.6]

Cumulative incidence of atopic comorbidities at 10 years of follow-up in patients with and without FPIES. *P* value is shown from the χ^2 test, followed by the Woolf-logit method to compute the unadjusted odds ratio.

CI, Confidence interval; FPIES, food protein–induced enterocolitis syndrome.

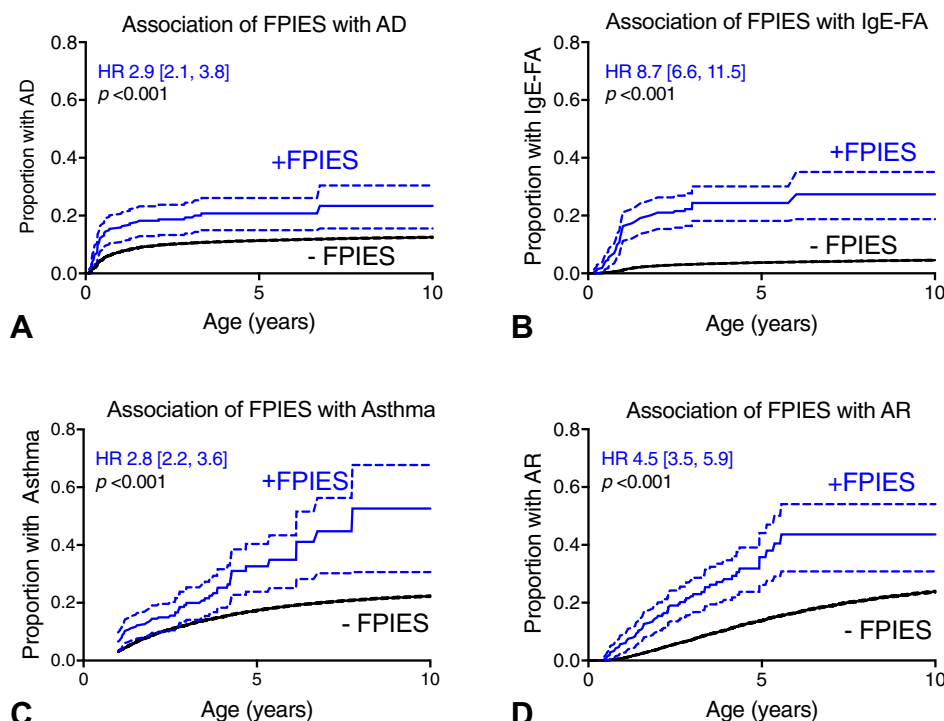


FIGURE 4. Development of atopy in FPIES and non-FPIES cohorts, irrespective of timing of FPIES onset. Kaplan-Meier curves and 95% confidence intervals (CI) displaying diagnosis of (A) atopic dermatitis (AD), (B) IgE-mediated food allergy (IgE-FA), (C) asthma, (D) allergic rhinitis (AR) in patients with FPIES or healthy controls. Hazard ratios (HR), 2.5% to 97.5% CI, and *P* values from logistic regression for each comparison are shown in each panel. FPIES, Food protein–induced enterocolitis syndrome.

Among grains, oat, rice, and wheat were the most common eliciting allergens (Figure 3, B). White potato and corn accounted for the majority of vegetable triggers (Figure 3, C), though we also observed avocado as a prominent trigger consistent with recent reports.^{18,24} FPIES reactions were observed to a variety of meats including beef, chicken, turkey, pork, and lamb (Figure 3, D).

FPIES presentations can be classified as either acute or chronic.⁶ The majority of patients in our cohort (78%) presented with symptoms of acute FPIES, with the remaining patients meeting criteria for chronic FPIES (Figure 3, E). Consistent with prior studies, chronic FPIES was diagnosed in infants in our cohort between 1 and 4 months of age.⁷ Regardless of presentation type, it was most common for patients to have a single FPIES food trigger (Figure 3, E). However, some patients with symptoms to multiple food triggers were also observed. In the

case of chronic FPIES to multiple foods, 59.2% of patients reacted to milk alone, 8.2% to soy alone, and 32.6 to milk and soy.

We and others have previously reported earlier onset of acute FPIES to milk and soy as compared with solid foods.^{1,17,18} Consistent with this observation, children presenting with acute FPIES triggered by milk or soy in our primary care birth cohort were more likely to present with FPIES at an earlier age (median age, 3 months) when compared with those with acute FPIES to solid foods (median age, 6 months, *P* < .001, Figure 3, F). FPIES to milk and soy is commonly seen before the onset of solid foods, and it is hypothesized that this relates to the order in which these foods are introduced during weaning.^{1,17,18} Together, these data highlight the similarities of our FPIES cohort patients' clinical presentations to that of other cohorts described in North America.

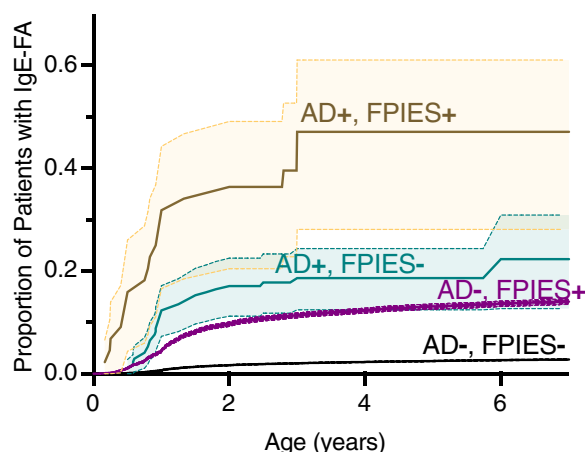


FIGURE 5. Interaction of FPIES and atopic dermatitis (AD) on development of IgE-mediated food allergy (IgE-FA). Kaplan-Meier curves and 95% confidence intervals from the analysis of IgE-FA development in patients with or without FPIES (as a categorical variable) or AD. FPIES, Food protein–induced enterocolitis syndrome.

Relationship between FPIES and the atopic conditions

We next examined the degree of atopic comorbidity in patients with FPIES using χ^2 testing (Table II). When comparing patients with FPIES to healthy controls, the prevalence of IgE-FA was increased approximately 6-fold (23.8% vs 4.0%; odds ratio [OR], 10.5 [5.5–10.4]). The prevalence of AD was nearly 2-fold higher in patients with FPIES compared with controls (20.6% vs 11.7%; OR, 2.0 [1.5–2.7]). Lastly, asthma and AR had a relatively smaller increase in cumulative incidence within the FPIES cohort, but were still significantly increased when compared to patients without FPIES (asthma 26.6% vs 18.4%; OR, 1.6 [1.2–2.2]; AR 28.0% vs 16.7%; OR, 1.9 [1.4–2.6]). These findings are consistent with prior reports that have also found a high burden of atopy in patients with FPIES.²⁵

As retrospective analyses of disease cohorts are subject to several forms of bias, we next sought to examine the temporal relationships between FPIES onset and the development of atopy. To do so, we used Cox proportional hazard modeling that incorporated patient birth year, race, ethnicity, sex, and insurance status as covariates. We first examined the onset of AD, IgE-FA, asthma, and AR in the FPIES and non-FPIES cohorts, irrespective of the timing of FPIES diagnosis (eg, FPIES onset could precede or follow atopic diagnosis). FPIES cohort patients develop atopy at a higher rate than healthy controls (Figure 4), an observation that is consistent with patients with FPIES having a high burden of atopic disease.²⁵ As these data suggest that FPIES accelerates the rate of atopic disease development, we next explored the impact of coexisting FPIES and atopic dermatitis on the rate of IgE-FA development. We observe that FPIES is associated with increased risk of IgE-FA, regardless of if patients had comorbid atopic dermatitis (Figure 5). Furthermore, FPIES confers additional risk for the development of IgE-FA than atopic dermatitis alone (hazard ratio, 4.3 [2.7, 6.8] in AD–, FPIES+ vs FPIES– patients). The majority of patients with FPIES had comorbid IgE-FA to one type of eliciting allergen (Figure 6, A),

and the most common IgE-FA triggers in patients with FPIES were egg, peanut, milk, and tree nuts (Figure 6, B).

Next, we sought to understand whether a history of FPIES increases one's risk of developing subsequent atopy. To do so, we examined the rate of atopy development in patients with a preceding FPIES diagnosis. With the requirement that FPIES diagnosis precedes the development of atopy, we observed no significant difference in the rate of onset of the atopic outcome in the FPIES and non-FPIES cohort (Figure 7). Similarly, if FPIES is required to precede the diagnosis of IgE-FA, only AD remains a significant determinant of IgE-FA development (data not shown). Therefore, although there is increased atopic comorbidity in patients with FPIES, our analyses demonstrate that in contrast to the relationship observed in the atopic march,²² a prior diagnosis of FPIES does not increase the rate of subsequent atopy development.

CONCLUSIONS

FPIES is increasingly recognized as a cause of food allergy in young children.²⁶ Here, we provide a large, retrospective study of physician-diagnosed FPIES within a primary care-based pediatric cohort. Several of our findings are consistent with prior observations in subspecialty-based cohorts. In particular, males and whites were diagnosed with FPIES slightly more frequently than females and other races, and the most common foods causing FPIES were milk, soy, oat and rice.^{1,6,15,17,18} In addition, age of disease presentation was significantly older in patients who reacted to solid foods, as opposed to those who reacted to milk and soy.¹ The similarities between our current cohort, and those that have been previously described, suggest that our methods accurately identified patients with FPIES.

Using incidence density analysis across patient age, we find the peak age of FPIES diagnosis to be at 6 months, followed by a period of relatively steady low incidence. Because of the variable observation times available for children in our cohort, it is possible that our analysis could fail to detect an additional late peak of disease onset. Our data indicate an average yearly incidence of FPIES of 0.008% after age 3, corresponding to a handful of observations of FPIES presentation in children above age 3 years within our cohort. Indeed, there are rare reports of *de novo* FPIES development in adolescents and adults.^{4,5,27} However, such cases are rare, and the majority of studies describe the onset of FPIES in infancy, and we also report peak incidence at 6 months of age.

We also observe a variable incidence across the study time period. Specifically, the incidence of FPIES diagnosis increases across the timespans from 2010 to 2014, and then again from 2015 to 2018. Several reasons may account for this increase in incidence. Although we have previously been able to identify FPIES cases using the nonspecific ICD-9 coding at our institution, implementation of the FPIES-specific diagnostic code in 2015 may have permitted us to better identify cases. This increase may also reflect growing provider awareness of the FPIES diagnosis. Lastly, we cannot exclude the possibility that the incidence of FPIES within our study population is increasing. Consistent with prior studies,^{14–19} we observe that the overall prevalence of atopic disease is higher in children with FPIES as compared with healthy children. A strength of our analysis compared with prior is that by comparing physician-diagnosed disease rates in a birth cohort, we can control for local medical

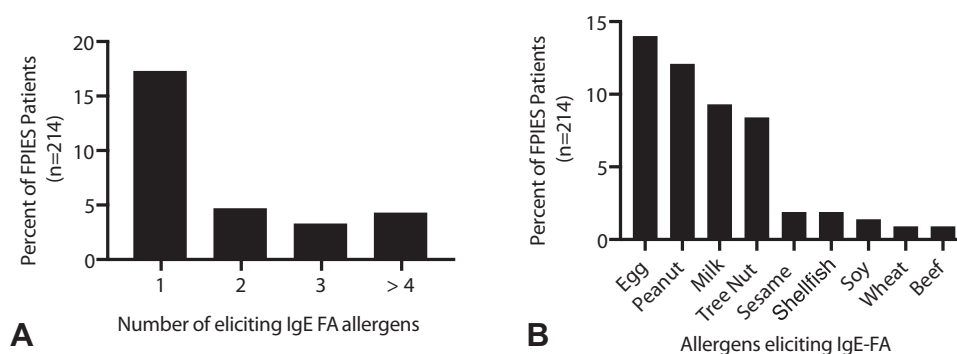


FIGURE 6. IgE food allergy triggers in patients with FPIES. **A**, Percent of total FPIES cohort patients with IgE-FA to 1, 2, 3, or 4 or more eliciting allergens. **B**, Percent of total FPIES cohort patients with IgE-FA to the eliciting allergens shown. *FPIES*, Food protein–induced enterocolitis syndrome; *IgE-FA*, IgE-mediated food allergy.

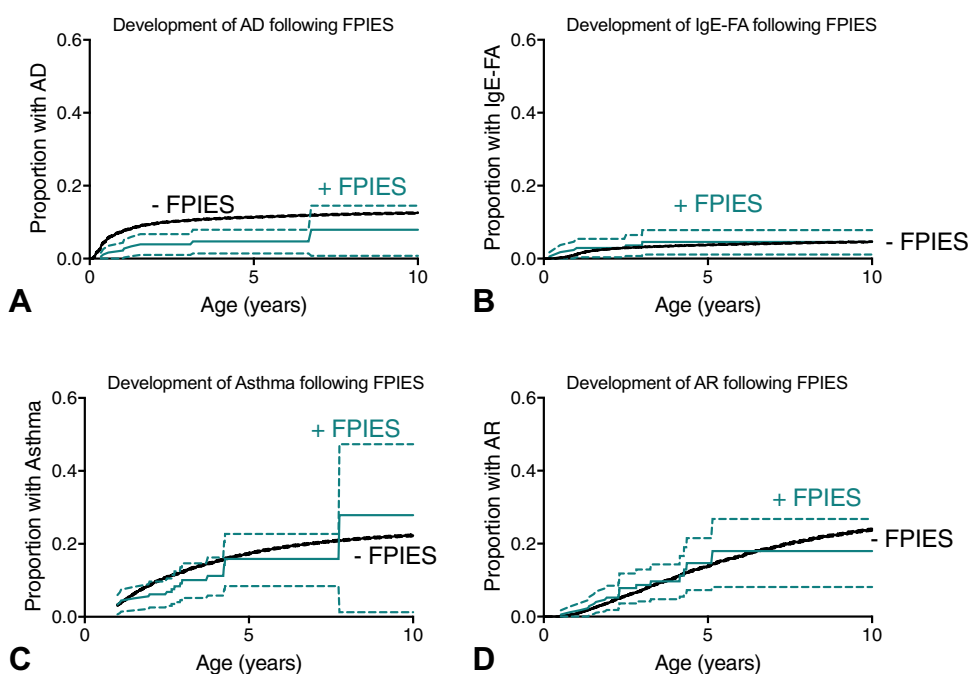


FIGURE 7. Development of atopy in patients with preceding FPIES. Kaplan-Meier curves and 95% confidence intervals displaying diagnosis of **(A)** atopic dermatitis (AD), **(B)** IgE-mediated food allergy (IgE-FA), **(C)** asthma, **(D)** allergic rhinitis (AR) in patients with FPIES or healthy controls. *FPIES*, Food protein–induced enterocolitis syndrome.

practice patterns. As such, our estimates likely represent more accurate measures of the epidemiologic features of FPIES, and the degree of disease comorbidity between FPIES and the atopic conditions when compared with prior studies.

However, when interpreting these findings it is important to consider possible mechanisms of disease association: chance, selection bias, and causal association.²⁸ The association between FPIES and atopy has been demonstrated across multiple studies in diverse patient cohorts, making the association unlikely to be a result of chance alone. When considering bias, there are several forms that may contribute to the observed associations. Examinations of subspecialty cohorts are susceptible to subject selection bias, ascertainment bias, and provider bias, as allergists may be more likely to diagnose atopic comorbidities in patients with

FPIES, or may diagnose the complications at a younger age than a general practitioner. The use of a primary care cohort in our study helps to negate some of these biases, with the caveat that many patients with FPIES are still referred to allergists. Although clinician choice of diagnosis codes can be a source of potential bias, a strength of our analysis is the use of physician-entered diagnosis codes and manual chart review to identify patients with FPIES.

Having considered the effects of chance and bias, one can consider an etiological association between FPIES and atopy. Four broad categories of etiology exist: direct causation, associated risk factors, heterogeneity, and independence.²⁸ These groups are not mutually exclusive; one or more can contribute to a disease association as is likely the case with the atopic

march.^{13,21} Although it is not possible to establish causality using a study such as this one, one can determine the temporal features of an association to support or refute a particular etiologic category. This is particularly relevant to direct causation where an initial disease process is a direct cause of a second, subsequent disease (eg, diabetes mellitus and cataracts).²⁸ In this etiological group, the causative feature(s) of the initial disease must occur before the development of the second, subsequent disease.

To understand the temporal relationship between FPIES and the atopic conditions, we performed 2 longitudinal examinations. First, we measured the rate of atopy in patients with FPIES irrespective of the timing of FPIES diagnosis. In this first approach, we observed that patients with FPIES have a higher rate of development of atopic comorbidity as compared with non-FPIES patients. However, when we constrain this analysis to examine if a preceding FPIES diagnosis alters the rate of atopic manifestations, we observe that patients with a preceding FPIES diagnosis develop atopy at the same rate as the birth cohort population. In other words, although the atopic burden is higher among patients with FPIES, a preexisting FPIES diagnosis does not increase one's risk for development of subsequent atopy. This temporal relationship is not consistent with direct causation as a mechanism of etiological association between these conditions. Rather, this pattern of association supports a yet unknown etiology such as shared predisposition to both types of allergy. This association could also be explained by the effect of bias confounding the analysis. Together, these data improve our understanding of the true epidemiologic relationships between FPIES and the atopic manifestations.

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