Real-World Analysis Of Prevalence, Patient Characteristics, And Healthcare Resource Utilization And Costs (HRUC) Among Children with Food Protein-Induced Enterocolitis Syndrome (FPIES) In The United States (US)

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Background

- Food protein-induced enterocolitis syndrome (FPIES) is a non-immunoglobulin E (IgE)–mediated food allergy that presents with severe vomiting 1 to 4 hours after food ingestion accompanied by lethargy, diarrhea, dehydration, and sometimes shock. Common trigger foods include cow's milk, soy, and grains (like rice and oat), but any food can cause FPIES.[1,2]
- Awareness of FPIES is low. An International Classification of Diseases (ICD) code specific to FPIES was first introduced in October 2016 (ICD10 K52.2), and standards for the diagnosis and management of FPIES are beginning to be published. Unlike IgE-mediated allergies, there is no FDA-approved diagnostic test or treatment for FPIES.[1,2]
- This study is the first to examine FPIES patients using healthcare claims data.

Objective

- To estimate the prevalence of FPIES among children ages 0-3; characterize their patient characteristics, diagnosis, and management; and describe their healthcare resource utilization and costs in the United States.

Methods

Study Design and Patients

- Yearly (2017-2020) prevalence was estimated as the proportion of persons with a FPIES diagnosis (ICD 10th revision code K52.2) among total persons aged 0-3 years (0-47 months) with at least one day of enrollment using the MarketScan® Commercial Database.
- For retrospective analysis, children aged 0-3 years with a FPIES diagnosis between January 1st, 2017 and March 31st, 2021 and database enrollment (with medical and pharmacy benefits) for 6 months after diagnosis (follow-up period).
- A control cohort of children aged 0-3 years without evidence of FPIES during the study period and meeting the same enrollment criteria as the FPIES cohort was also selected (index date randomly assigned according to distribution of index dates observed in the FPIES cohort).

Assessments

- Healthcare resource utilization and costs (HRUC), provider specialties visited, and FPIES-related diagnoses, procedures, and medications were reported for the FPIES cohort compared with matched controls during the 6-month follow-up period.
- Conditions for which FPIES is commonly misdiagnosed were reported (among the subsets with pre-diagnosis enrollment).

Statistical Analyses

- FPIES children were matched directly to non-FPIES controls on age (in months), sex, and index year (10 controls per case).
- Chi-square tests were used to evaluate statistical significance for differences in categorical variables; t-tests were used to analyze continuous variables.

Results

Prevalence Analysis

- The prevalence of FPIES among children aged 0-3 increased steadily from 0.06% in 2017 to 0.17% in 2020 (Figure 1).

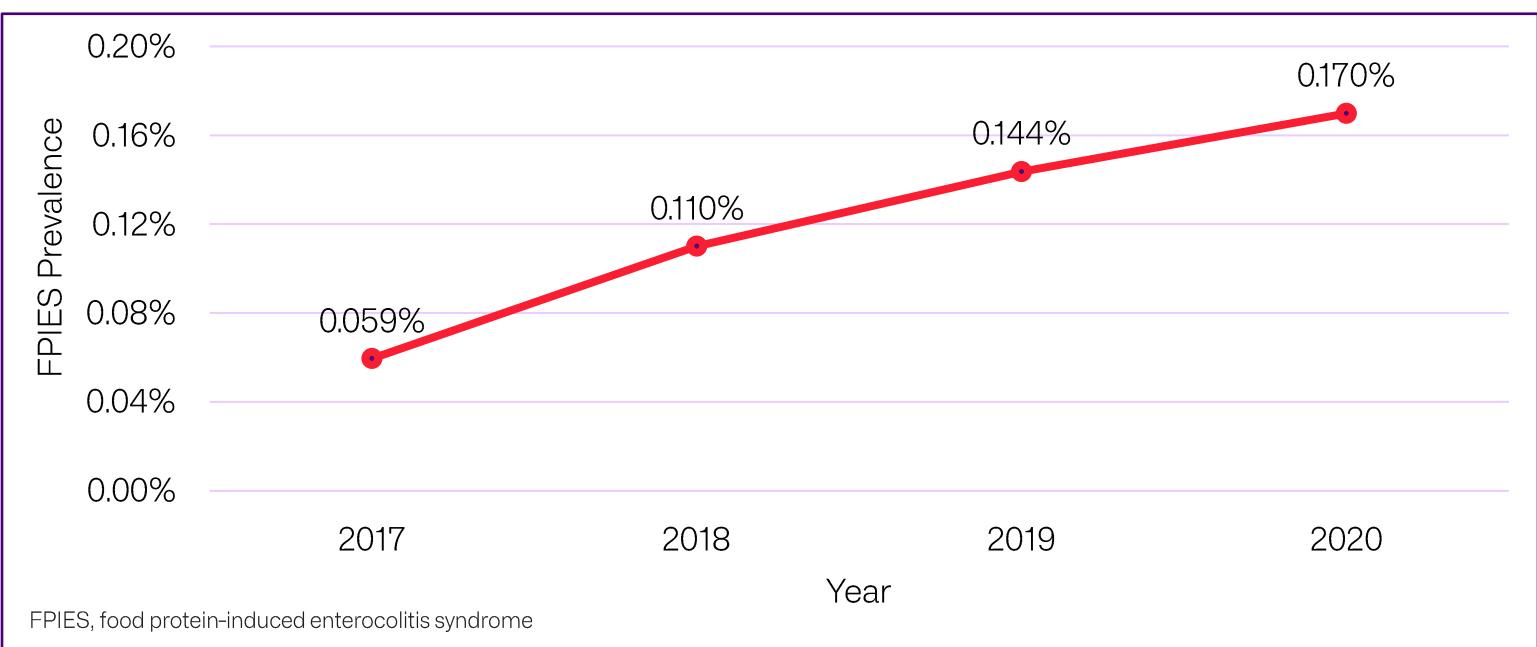### Figure 1. Prevalence of FPIES Among Children Ages 0 to 3

FPIES, food protein-induced enterocolitis syndrome

Figure 2. Age at FPIES Diagnosis Date (Index)
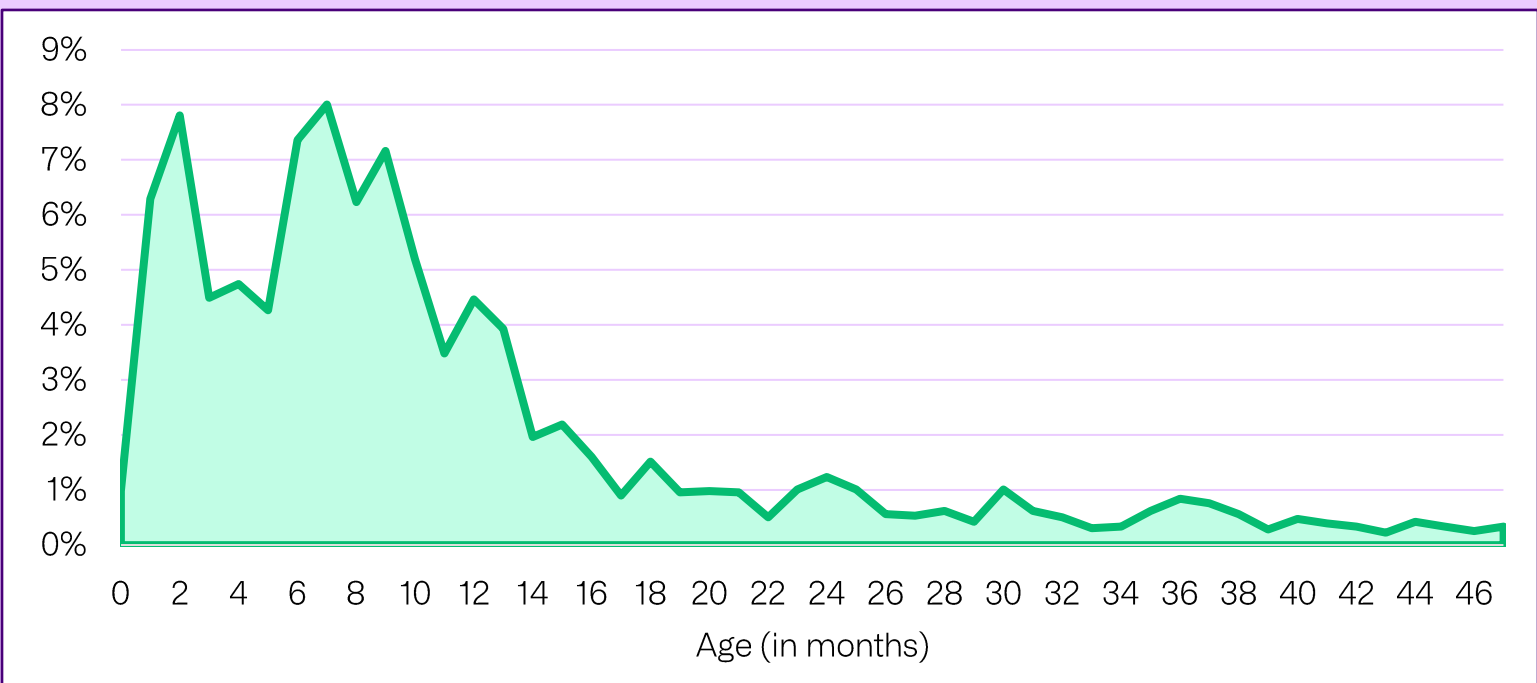
Table 1. Diagnosis and Treatment Patterns

	FPIES Cohort N=3,561	Matched Controls N=35,610	P-value
Specialties visited on FPIES diagnosis date (index)*, N (%)			
Allergy & immunology	1,164 (32.7%)		
Gastroenterology	278 (7.8%)		
Pediatrician	1,406 (39.5%)		
Emergency medicine	50 (1.4%)		
Primary care	293 (8.2%)		
None of the above	455 (12.8%)		
Specialties visited during follow-up, N (%)			
Allergy & immunology	1,620 (45.5%)	851 (2.4%)	<0.001
Gastroenterology	720 (20.2%)	479 (1.3%)	<0.001
Pediatrician	3,110 (87.3%)	27,653 (77.7%)	<0.001
Primary care	1,057 (29.7%)	9,988 (28.0%)	0.041
Nutritionist	193 (5.4%)	396 (1.1%)	<0.001
Diagnoses during follow-up, N (%)			
Anemia	143 (4.0%)	708 (2.0%)	<0.001
Asthma	150 (4.2%)	711 (2.0%)	<0.001
Atopic dermatitis	525 (14.7%)	1,670 (4.7%)	<0.001
Conjunctivitis	288 (8.1%)	2,393 (6.7%)	0.002
Failure to thrive	251 (7.0%)	678 (1.9%)	<0.001
IgE-mediated food allergy	1,385 (38.9%)	1,139 (3.2%)	<0.001
Rhinitis	285 (8.0%)	1,465 (4.1%)	<0.001
Prescriptions during follow-up, N (%)			
Epinephrine	314 (8.8%)	375 (1.1%)	<0.001
Infant formula	27 (0.8%)	14 (0.0%)	<0.001
Nystatin	286 (8.0%)	2,197 (6.2%)	<0.001
Ondansetron	491 (13.8%)	833 (2.3%)	<0.001
Prednisolone/methylprednisolone	243 (6.8%)	1,872 (5.3%)	<0.001
Ranitidine	305 (8.6%)	978 (2.7%)	<0.001
Procedures during follow-up, N (%)			
Allergy tests, other than oral food challenge**	1,458 (40.9%)	1,011 (2.8%)	<0.001
Colonoscopy	20 (0.6%)	8 (0.0%)	<0.001
Endoscopy	79 (2.2%)	52 (0.1%)	<0.001
Oral food challenge	234 (6.6%)	99 (0.3%)	<0.001

FPIES, food protein-induced enterocolitis syndrome; IgE, Immunoglobulin E; sIgE, specific IgE.
*Children in the FPIES cohort may have visited more than one specialty on the index date (the categories are not mutually exclusive). FPIES children were included in the "none of the above" category if they did not visit any of the listed specialties on the index date.
**Includes: skin prick test, patch test, serum food sIgE test, etc.

Figure 3. Conditions for Which FPIES is Commonly Misdiagnosed Measured Prior to Index Date*
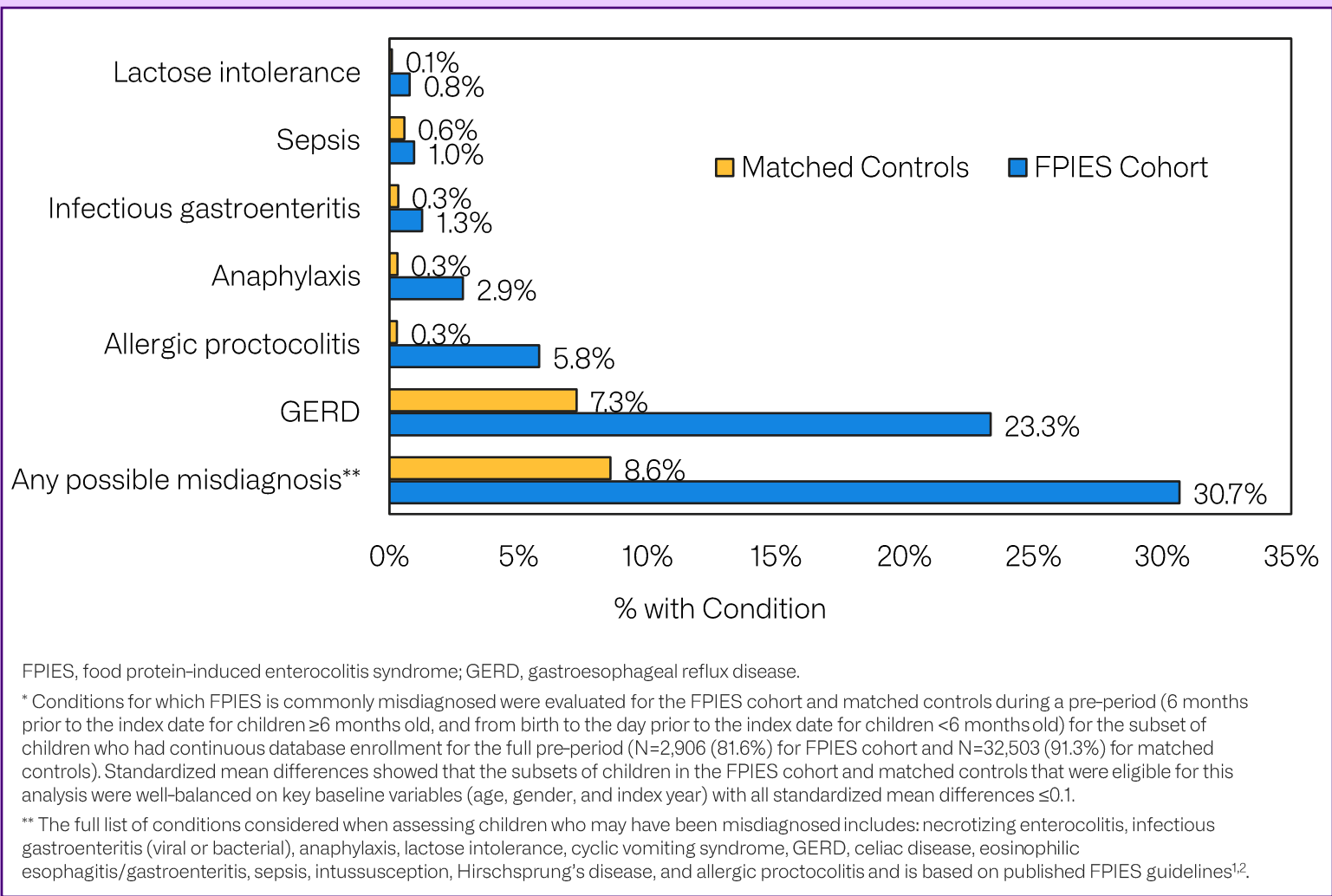

FPIES, food protein-induced enterocolitis syndrome; GERD, gastroesophageal reflux disease.
* Conditions for which FPIES is commonly misdiagnosed were evaluated for the FPIES cohort and matched controls during a pre-period (6 months prior to the index date for children ≥6 months old, and from birth to the day prior to the index date for children <6 months old) for the subset of children who had continuous database enrollment for the full-period (N=2,906 (81.6%) for FPIES cohort and N=32,503 (91.3%) for matched controls). Standardized mean differences showed that the subsets of children in the FPIES cohort and matched controls that were eligible for this analysis were well-balanced on key baseline variables (age, gender, and index year) with all standardized mean differences ≤0.1.
** The full list of conditions considered when assessing children who may have been misdiagnosed includes: necrotizing enterocolitis, infectious gastroenteritis (viral or bacterial), anaphylaxis, lactose intolerance, cyclic vomiting syndrome, GERD, celiac disease, eosinophilic esophagitis/gastroenteritis, sepsis, intussusception, Hirschsprung's disease, and allergic proctocolitis and is based on published FPIES guidelines[1,2].

Figure 4. Emergency Room Visits Measured Over 6 Months of Follow-Up*

ER, emergency room; Food protein-induced enterocolitis syndrome; OP.
* The inner circle shows the % of children in the FPIES cohort and the matched controls who had at least one ER visit during the 6-month follow-up period. The outer circle shows the % of children with a given number of ER visits (1, 2, 3, 4, and 5+) among those with at least one ER visit.
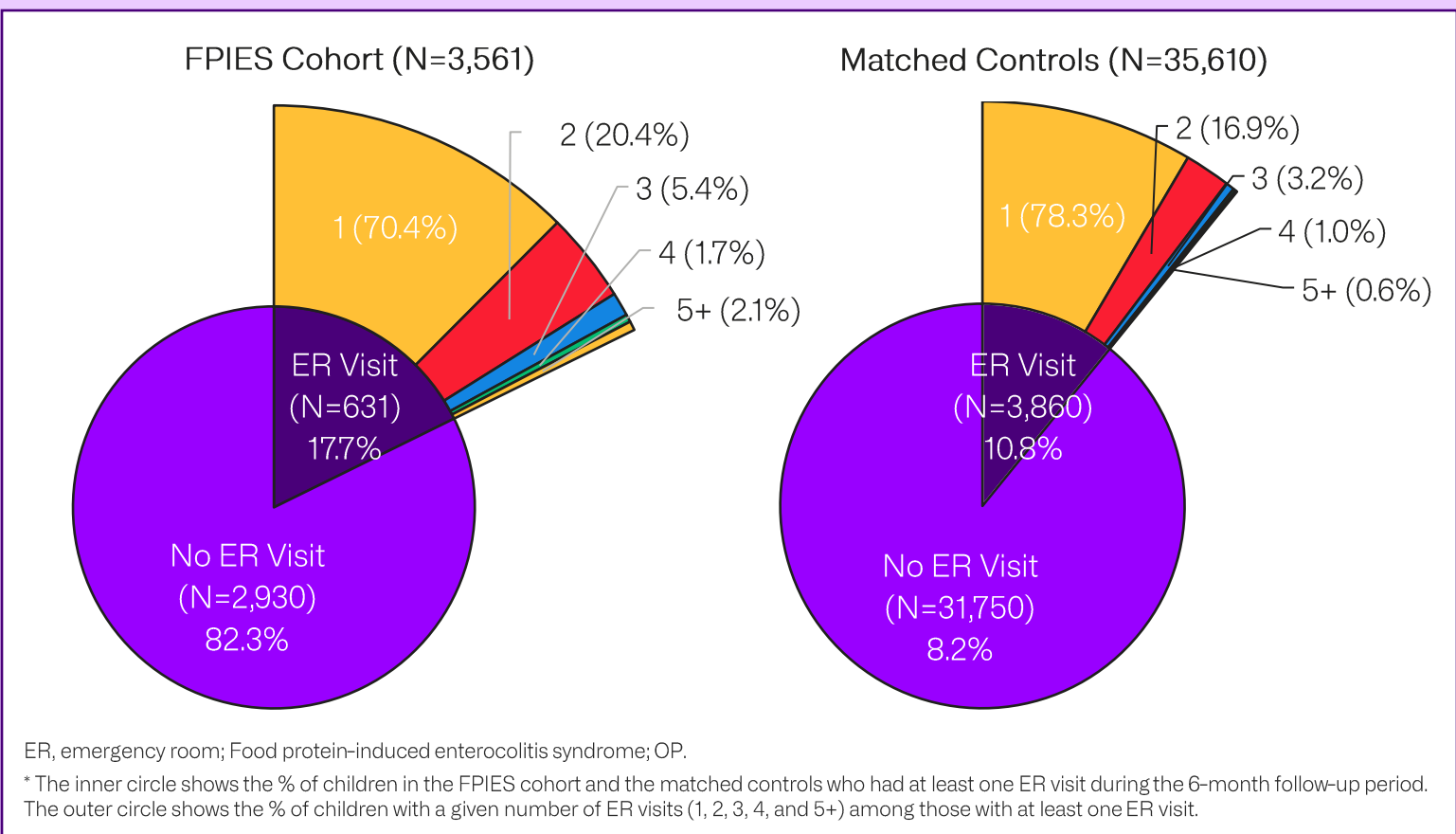
Figure 5. Healthcare Costs Measured Over 6 Months of Follow-Up*

ER, emergency room; FPIES, Food protein-induced enterocolitis syndrome; OP, outpatient.
* Differences between FPIES cohort and matched controls for service categories are statistically significant with P<0.035 for IP costs and P<0.001 for all others.
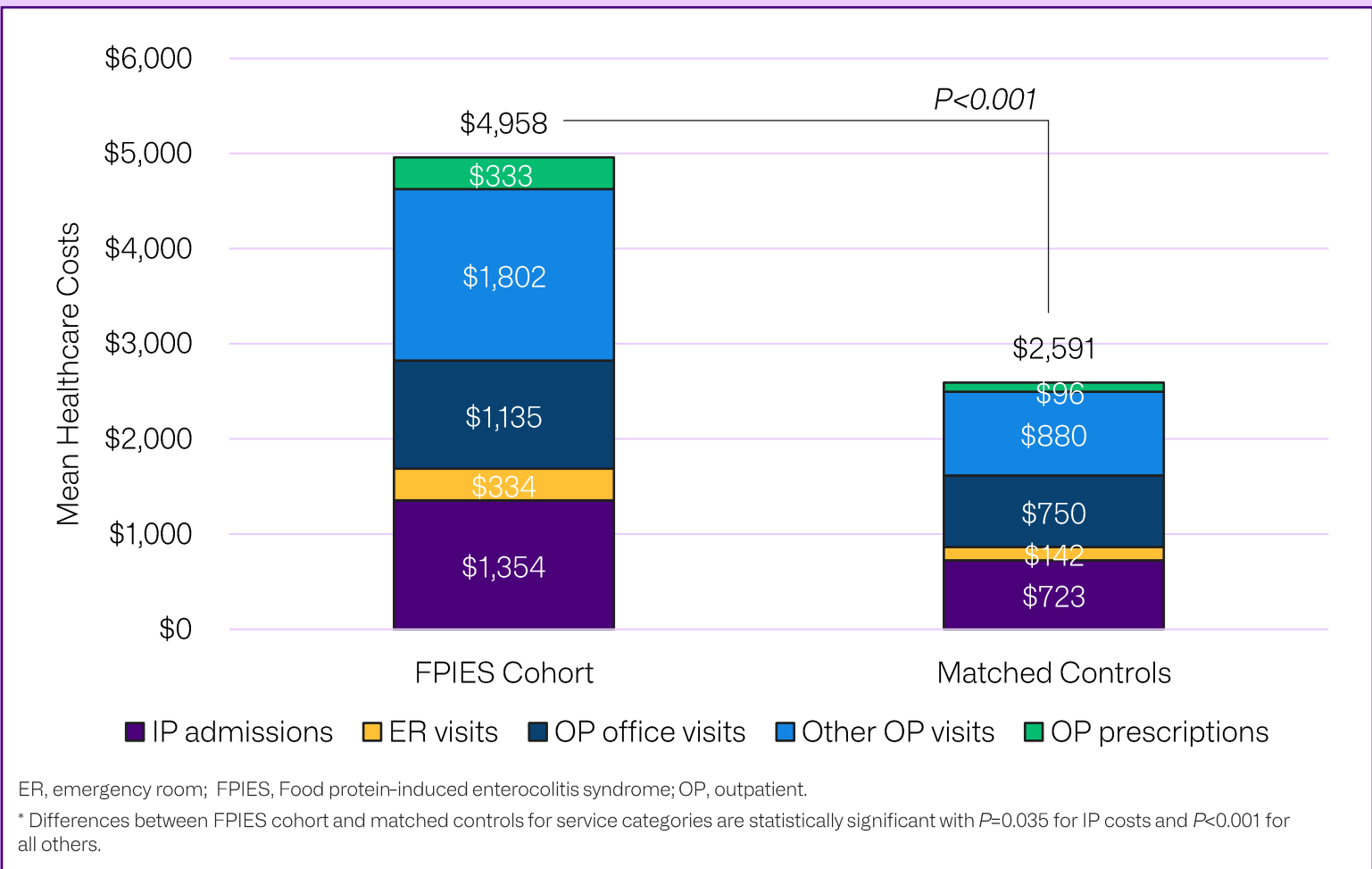
Results (cont.)

Retrospective Analysis – Study Population

- Overall, 3,561 children with FPIES and 35,610 matched controls were included in the retrospective analysis.
- The median age of children with FPIES was 8 months.
  - Many children were either 2-3 months or 6-9 months old, coinciding with the ages at which infant formula (milk/soy-based) and solid foods are often introduced (Figure 2).
- 52.1% of children with FPIES were male.

Retrospective Analysis - Diagnosis and Treatment Patterns

- On their FPIES diagnosis date (index), most children with FPIES were seen by a pediatrician (39.5%) or allergist (32.7%). During follow-up, a larger proportion of children with FPIES saw allergists (45.5% vs. 2.4%; P<0.001), gastroenterologists (20.2% vs. 1.3%; P<0.001), and nutritionists (5.4% vs. 1.1%; P<0.001) compared with matched controls (Table 1).
- A larger proportion of children with FPIES had evidence of failure to thrive (7.0% vs. 1.9%; P<0.001), atopic dermatitis (14.7% vs. 4.7%; P<0.001), and IgE-mediated food allergies (38.9% vs. 3.2%; P <0.001) compared with matched controls (Table 1).
- Children with FPIES were more likely to have a condition for which FPIES is commonly misdiagnosed (30.7% vs. 8.6%; P<0.001) compared with matched controls (Figure 3).
  - The most commonly observed misdiagnosis conditions among children with FPIES were gastroesophageal reflux disease (GERD; 23.3%), allergic proctocolitis (5.8%), anaphylaxis (2.9%), infectious gastroenteritis (1.3%), sepsis (1.0%), and lactose intolerance (0.8%).

Retrospective Analysis - All-cause Healthcare Resource Utilization and Costs

- A larger proportion of children with FPIES had ER visits (17.7% vs. 10.8%; P<0.001) compared with matched controls, with ~30% having 2 or more ER visits during the 6-month follow-up (Figure 4).
- Children with FPIES had significantly higher healthcare costs overall ($4,958 vs. $2,591; P<0.001) and in each of the services categories (i.e., inpatient, outpatient, and pharmacy) compared with matched controls (Figure 5).

Limitations

- The prevalence of FPIES is likely higher than what is reported in this analysis since many FPIES cases have gone undiagnosed.
- Likewise, this analysis may reflect a sicker FPIES population (children with more severe disease may be more likely to be diagnosed) that may have different treatment patterns and higher healthcare burden compared to the general FPIES population.

Conclusions

- The prevalence of FPIES is increasing as disease awareness grows.
- This real-world analysis found that children with FPIES have nearly double the healthcare costs of other children their age.
- Future research is needed to better understand which practice / prescribing patterns are most effective for diagnosis and management of FPIES to assist practitioners in their care of children with FPIES.

References
1. Nowak-Wegrzyn A, Chehade M, Groetch ME, 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 Apr;139(4):1111-1126.e4.
2. International FPIES Association, https://www.fpies.org/ Accessed 14 March 2023.

Disclosure
MJ and NP are employees of Merative.

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