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# Food protein-induced enterocolitis syndrome in the US-population-based study

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## Capsule summary:

FPIES affects estimated 0.5% of US children and 0.2% of adults (approximately 900,000 people). These data suggest that comprehensive epidemiologic studies are needed to better characterize the public health burden of FPIES.

### Keywords

Food allergy; food protein-induced enterocolitis syndrome; FPIES; children; adults; prevalence; epidemiology

## To the Editor:

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE, cell-mediated food allergy that manifests with repetitive, projectile vomiting within 1–4 hours following food ingestion, frequently accompanied by pallor, lethargy and may be followed by diarrhea within 6–8 hours.[1] In about 15–20% of the reactions, severe dehydration with hypotension and metabolic derangements are present.[1] FPIES diagnosis may be delayed due to the

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severity, delayed onset of symptoms and lack of cutaneous and respiratory manifestations (e.g., hives, wheezing), typically associated with IgE-mediated food allergy, and food triggers considered to have low allergenic potential, e.g. rice, oat, fruits, and vegetables. FPIES usually starts in the first year of life; the most commonly reported triggers in infants in the US include cow's milk, soy, rice and oat, followed by fruits, vegetables and egg. In adults, fish and shellfish are common triggers.[2] While FPIES prognosis is generally favorable, with most children becoming tolerant to the trigger food by age 3–5 years, FPIES has a significant negative impact on the quality of life of the caregivers (greater than that of IgE-mediated food allergy), is associated with feeding difficulties and with increased financial costs to the affected families.[3]

FPIES is regarded as a rare food allergy disorder. There are no data on the prevalence of FPIES in the US but over the past decade, many peer-reviewed reports were published characterizing clinical phenotypes, natural history, and providing insights into pathophysiology of FPIES. Patient organizations were established in response to a growing number of caregivers seeking support. In 2017, the first international consensus guidelines for FPIES diagnosis and management were published.[1] Data derived from single center birth cohorts from Israel and Spain estimated cumulative incidence rates of FPIES in infancy between 0.34–0.7%. [4,5] In contrast, a national study of pediatric disease surveillance data with utilization of a questionnaire and a strict case definition estimated a cumulative incidence rate of 0.015% among Australian infants.[6] Collectively, these data suggest that FPIES is more common than appreciated.

We sought to provide the first estimate of the lifetime prevalence of FPIES in the US by analyzing data from study designed to estimate the US population-level prevalence and distribution of IgE-mediated food allergy based on a large, nationally-representative sample of US households.

A cross-sectional, population-based survey was administered between October 2015 and September 2016 to a sample of 53,575 US households. Informed consent was obtained from all participants. The Northwestern University IRB approved all study activities. Methodological details about survey development, complex survey sampling and weighting have been previously described. [7–9]

The outcome measure of interest was the lifetime prevalence of physician-diagnosed FPIES. Participants were asked: "Have you/Has your child ever been diagnosed by a physician with food protein-induced enterocolitis syndrome (FPIES)? Note, this is a very specific and rare allergic condition". Questions about the presence of other chronic atopic comorbidities utilized the same question stem. The survey did not include specific questions regarding symptoms, food triggers, age at diagnosis and whether FPIES was resolved or active.

In addition, we analyzed the reported physician-diagnosed food allergy (IgE-mediated, IgE-food allergy), asthma, atopic dermatitis (AD), and allergic rhinitis (AR) as per the definitions published previously. [7–9] Eligible study participants included adults (≥18 years old) able to complete the survey in English or Spanish via web or telephone, who resided in a US household.

Point prevalence estimates were based on participants recruited from NORC at the University of Chicago's, probability-based *AmeriSpeak Panel*, with a survey completion rate of 51.2%. To improve the precision of estimates, these data were augmented via small-area estimation with additional participants recruited from *Survey Sampling International*. Prevalence estimates were calculated using Stata 14 via complex survey-weighted proportions.

**Children:**

Parent proxy-report data were collected for 38,408 children.[7] In total, 261 children with FPIES were reported, estimated prevalence 0.51% (95% CI; 0.42–0.62), Table I. Children with FPIES were more likely to be of Asian/non-Hispanic race/ethnicity and had significantly higher rates of parent-reported-IgE-FA (meeting stringent symptoms-report criteria for reaction), as well as other allergic diseases, compared to children without FPIES, shown in Table II. Thirteen families (4.9%) reported multiple children with FPIES; 5 children (1.9%) had a parent (in all cases a father) with FPIES.

**Adults:**

Self-report data were collected for 40,443 adults, as published.[9] In total, 113 adults reported physician-diagnosed FPIES, estimated prevalence 0.22% (95% CI; 0.17–0.28), Table I. Adults with FPIES had significantly higher rates of reported-IgE-FA, as well as other allergic diseases, compared to adults without FPIES (Table II).

Based on population-weighted estimates obtained from this nationally-representative sample, physician-diagnosed FPIES was reported by an overall 0.28% (0.24–0.33%) of Americans, corresponding to over 900,000 people. The FPIES prevalence estimate of 0.51% (95% CI; 0.420.62) reported for US children is in line with data from the single center population-based birth cohorts from Israel and Spain, reporting cumulative incidence 0.34% and 0.7% respectively.[4,5] Our study provides the first ever estimate of FPIES prevalence in adults. To date, only several small case series of adult patients were published. [2]

Our report has several limitations. The survey was not developed to estimate FPIES prevalence and details of the trigger foods and symptoms are lacking. While the survey asked about physician-diagnosed FPIES, specific case definition wasn't provided; we have no information about the diagnostic criteria used, and whether oral food challenges were performed to confirm diagnosis. Therefore, it is possible that FPIES diagnosis was used incorrectly due to the poor familiarity of the physicians with FPIES and led to under or over-estimation of true FPIES prevalence. This cross-sectional study captures patients reporting lifetime FPIES, therefore we do not know which patients may or may not have outgrown FPIES and if there is any difference in those who do and those who do not outgrow.

These data suggest that FPIES affects nearly one million people in the US and the FPIES prevalence estimates are consistent with reports from Spain and Israel and not greatly different from the Australian estimates. Our data indicate the need for further epidemiologic studies to better characterize the population-level burden of FPIES in the US.

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**TABLE I.**

Estimated prevalence of FPIES in the US population

| Reported physician diagnosed current or past FPIES | Prevalence estimate (95% CI) |
|---|---|
| All ages, N=374 | 0.28 (0.24–0.33) |
| **Children** | |
| Age <18 years N=261 | 0.51 (0.42–0.62) |
| < 1 year (N=6) | 0.11 (0.04–0.26) |
| 1 year (N=17) | 0.59 (0.32–1.08) |
| 2 years (N=20) | 0.76 (0.39–1.47) |
| 3–5 years (N=41) | 0.52 (0.29–0.93) |
| 6–10 years (N=74) | 0.56 (0.40–0.78) |
| 11–13 years (N=58) | 0.61 0(.43–0.88) |
| 14–17 years (N=45) | 0.37 (0.24–0.57) |
| **Adults** | |
| Age ≥18 years, N=113 | 0.22 (0.17–0.28) |
| 18–29 (N=38) | 0.33 (0.22–0.49) |
| 30–39 (N=29) | 0.26 (0.16–0.43) |
| 40–49 (N=15) | 0.21 (0.11–0.43) |
| 50–59 (N=12) | 0.11 (0.06–0.21) |
| 60+ (N=19) | 0.18 (0.10–0.30) |

**TABLE II.**

Sociodemographic characteristics and comorbidities in children and adults

| | % among those with FPIES (95% CI) | % among those without FPIES (95% CI) | P value |
|---|---|---|---|
| **Children** | | | |
| ***Race/ethnicity*** | | | |
| Asian, non-Hispanic | 8.1 (4.2–15.1) | 3.2 (2.8–3.7) | 0.02 |
| Black, non-Hispanic | 16.3 (10.5–24.3) | 13.2 (12.3–14.2) | |
| White, non-Hispanic | 44.1 (34.9–53.8) | 52.9 (51.3–54.4) | |
| Hispanic | 27.8 (19.4–38.2) | 24.1 (22.5–25.7) | |
| Multiple/other | 3.7 (1.7–8.1) | 6.7 (6.1–7.3) | |
| ***Country of Origin*** | | | |
| Born in US | 95.8 (87.6–98.7) | 97.8 (97.4–98.1) | 0.26 |
| ***Sex*** | | | |
| Female | 47.7 (38.5–57.2) | 48.9 (47.8–50.0) | 0.81 |
| ***Age*** | | | |
| <1 year | 1.1 (.5–2.7) | 5.4 (4.8–5.9) | 0.15 |
| 1 year | 5.6 (3.1–10.1) | 4.9 (4.4–5.3) | |
| 2 year | 8.6 (4.5–15.8) | 5.7 (5.2–6.3) | |
| 3–5 years | 16.7 (9.9–26.8) | 16.2 (15.5–17.0) | |
| 6–10 years | 30.9 (23.1–39.9) | 27.8 (26.9–28.8) | |
| 11–13 years | 20.1 (14.4–27.3) | 16.6 (15.9–17.4) | |
| *14–17 years* | 17.0 (11.3–25.0) | 23.4 (22.4–24.4) | |
| ***Household income, $*** | | | |
| <25,000 | 16.8 (10.2–26.5) | 16.1 (14.9–17.3) | 0.85 |
| 25,000–49,000 | 20.0 (12.5–30.4) | 22.2 (20.9–23.5) | |
| 50,000–99,999 | 34.5 (26.6–43.3) | 31.1 (29.7–32.5) | |
| 100,000–149,000 | 20.3 (13.6–29.1) | 19.2 (18.0–20.5) | |
| ≥150,000 | 8.4 (4.4–15.6) | 11.4 (10.3–12.7) | |
| ***Physician-diagnosed comorbid atopic conditions*** | | | |
| ***Current*** | | | |
| IgE-mediated food allergy * | 65.3 (55.2–74.2) | 7.3 (6.9–7.8) | <0.001 |
| ***Lifetime*** | | | |
| Asthma | 25.2 (18.5–33.4) | 12.1 (11.3–13.0) | <0.001 |
| Atopic dermatitis/ eczema | 9.6 (5.8–15.5) | 5.9 (5.3–6.5) | 0.06 |
| Allergic rhinitis | 32.6 (24.4–42.0) | 12.7 (11.9–13.5) | <0.001 |
| Insect sting allergy | 5.0 (2.8–9.1) | 2.2 (1.9–2.6) | 0.007 |
| Latex allergy | 8.9 (5.3–14.6) | 1.0 (.8–1.2) | <0.001 |
| Medication allergy | 6.9 (4.1–11.4) | 4.1 (3.7–4.6) | 0.06 |
| Urticaria | 3.4 (1.−7.3) | 0.5 (.4-.6) | <0.001 |

| | % among those with FPIES (95% CI) | % among those without FPIES (95% CI) | P value |
|---|---|---|---|
| **Adults** | | | |
| ***Race/ethnicity*** | | | |
| Asian, non-Hispanic | 5.0 (2.4–10.2) | 3.9 (3.6–4.1) | 0.18 |
| Black, non-Hispanic | 13.8 (7.6–23.7) | 11.7 (11.3–12.1) | |
| White, non-Hispanic | 53.2 (41.2–65.0) | 64.9 (64.2–65.6) | |
| Hispanic | 24.4 (14.6–37.9) | 15.5 (14.9–16.1) | |
| Multiple/other | 3.6 (1.2–9.8) | 4.1 (3.8–4.4) | |
| ***Country of Origin*** | | | |
| Born in US | 87.1 (77.0–93.1) | 91.6 (91.2–92.0) | 0.18 |
| ***Sex*** | | | |
| Female | 53.5 (41.5–65.1) | 51.7 (51.0–52.4) | 0.77 |
| ***Age (years)*** | | | |
| 18–29 | 32.3 (22.4–44.2) | 21.4 (20.8–22.1) | 0.1 |
| 30–39 | 20.5 (12.8–31.4) | 17.0 (16.5–17.4) | |
| 40–49 | 16.6 (8.6–29.4) | 16.8 (16.3–17.3) | |
| 50–59 | 8.9 (4.5–16.9) | 18.0 (17.6–18.5) | |
| 60+ | 21.7 (13.1–33.6) | 26.8 (26.2–27.4) | |
| ***Household income, $*** | | | |
| <25,000 | 19.7 (12.2–30.2) | 16.6 (16.2–17.1) | 0.75 |
| 25,000–49,000 | 24.5 (16.0–35.5) | 21.9 (21.4–22.5) | |
| 50,000–99,999 | 29.6 (19.7–41.9) | 30.9 (30.3–31.5) | |
| 100,000–149,000 | 19.9 (11.3–32.7) | 19.6 (19.0–20.2) | |
| ≥150,000 | 6.3 (2.4–15.3) | 10.9 (10.4–11.5) | |
| ***Physician-diagnosed comorbid atopic conditions*** | | | |
| ***Current*** | | | |
| IgE-mediated food allergy | 42.5 (31.6–54.3) | 10.7 (10.3–11.1) | <0.001 |
| ***Lifetime*** | | | |
| Asthma | 37.4 (26.7–49.5) | 12.2 (11.8–12.7) | <0.001 |
| Atopic dermatitis/eczema | 22.3 (13.8–34.0) | 6.7 (6.4–7.0) | <0.001 |
| Allergic rhinitis | 31.1 (21.5–42.7) | 21.4 (20.9–22.0) | 0.047 |
| Insect sting allergy | 10.1 (4.5–21.0) | 3.8 (3.6–4.1) | 0.01 |
| Latex allergy | 13.1 (7.0–23.2) | 2.3 (2.1–2.5) | <0.001 |
| Medication allergy | 17.6 (9.4–30.5) | 13.4 (13.0–13.9) | 0.38 |
| Urticaria | 16.0 (8.5–28.1) | 0.8 (.7–1.0) | <0.001 |

There were no significant geographic differences in pooled pediatric and adult FPIES prevalence estimates based on US census region (p=.41) or division (p=.09), data not shown. A two-sided **p<0.05 was considered as statistically significant.**

* Indicates reported current FA with a history of reaction symptoms indicative of an IgE-mediated response.

** Indicates self-reported disease