

ORIGINAL ARTICLE

Food Allergy & Anaphylaxis

National trends in emergency department visits and hospitalizations for food-induced anaphylaxis in US children

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Abstract

Background: Food is the leading cause of anaphylaxis in children seen in emergency departments in the United States, yet data on emergency department visits and hospitalizations related to food-induced anaphylaxis are limited. The objective of our study was to examine national time trends of pediatric food-induced anaphylaxis-related emergency department visits and hospitalizations.

Methods: We conducted an observational study using a national administrative claims database from 2005 through 2014. Participants were younger than 18 years with an emergency department visit or hospitalization for food-induced anaphylaxis. Outcome measures of our study included time trends of pediatric food-induced anaphylaxis-related emergency department visits and hospitalizations, including observations (in an emergency department or a hospital unit), inpatient admissions, and intensive care unit admissions.

Results: During the study period, participants had 7310 food-induced anaphylaxis-related emergency department visits. Emergency department visits for food-induced anaphylaxis increased by 214% ($P < .001$); the highest rates were in infants and toddlers (age 0–2 years). Rates of emergency department visits significantly increased in all age-groups, with the highest increase in adolescents (age 13–17 years: 413%; $P < .001$). Peanuts accounted for the highest rates (5.85 per 100 000 in 2014) followed by tree nuts/seeds (4.62 per 100 000 in 2014). The greatest increase in rates of emergency department visits for food-induced anaphylaxis occurred with tree nuts/seeds (373.0% increase during the study period).

Conclusions: The incidence of food-induced anaphylaxis has significantly increased over time in children of all ages. Food-induced anaphylaxis in children is an important national public health concern.

KEYWORDS

children, epidemiology, food-induced anaphylaxis

Abbreviations: EAI, epinephrine autoinjector; ED, emergency department; FIA, food-induced anaphylaxis; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICU, intensive care unit; US, United States.

Portions of the Methods section have been previously published in Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Increasing emergency department visits for anaphylaxis, 2005–2014. *J Allergy Clin Immunol Pract*. 2017 Jan-Feb;5(1):171–175. Epub 2016 Nov 3. Used with permission.

1 | INTRODUCTION

Food-induced anaphylaxis (FIA) is the leading cause of anaphylaxis treated in emergency departments (EDs) in the United States (US).¹ FIA refers to a potentially fatal hypersensitivity reaction to ingested foods. FIA accounts for 30%–50% of anaphylaxis cases in the United

States,² in other developed countries in Europe,³ Asia,⁴ and in Australia.⁵

According to the Centers for Disease Control and Prevention, rates of food allergies in US children increased by about 50% between 1997 and 2011.⁶ Furthermore, the Centers for Disease Control and Prevention reported that approximately 10 000 children were hospitalized in the United States from 2004 to 2006 with a diagnosis of food allergy.⁷ This number was 3 times higher than previous estimates from 1998.

Comprehensive studies examining time trends are important for improving public awareness and directing public health initiatives to reduce morbidity and mortality. The objective of this study was to examine contemporary time trends related to ED visits and hospitalizations for FIA to better understand and characterize the burden of FIA in US children.

2 | METHODS

2.1 | Data source

This observational study used the OptumLabs Data Warehouse, which includes administrative claims data for more than 100 million privately insured and Medicare Advantage enrollees.⁸ The database contains longitudinal health information from geographically diverse regions across the United States spanning more than 20 years. The data cover multiple domains, including enrollee information (sex, age, race/ethnicity, dates of eligibility, and census region) and medical claims (including International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes).⁹ This study was deemed exempt from institutional review board approval because it involved analysis of pre-existing, deidentified data. The study followed standardized reporting guidelines (RECORD: REporting of studies Conducted using Observational Routinely-collected health Data).¹⁰

2.2 | Study population

Children younger than 18 years were included in this study. To identify the cohort of ED anaphylaxis visits from 2005 to 2014, we used 2 previously validated methods.¹¹ Method 1 identified patients with ICD-9-CM anaphylactic shock diagnosis codes (995.60-995.69 and 995.0). Method 2 identified patients through a validated algorithm of ICD-9-CM codes of symptom combinations.¹¹ At least 30 days of medical insurance coverage before the ED visit was required for inclusion in the study cohort. Similarly, medical insurance coverage for at least 30 days in the given calendar year was required for ED visits included in the denominator for rate calculations. ED visits identified by both methods were combined; duplicate visits were excluded.

2.3 | Food triggers

Specific food triggers were identified by the following associated ICD-9 CM codes: cow's milk (995.67), egg (995.68), peanuts (995.61),

tree nuts and seeds (995.64), crustaceans (995.62), fish (995.65), and others (995.69) which included fruits and vegetables (995.63). The ICD-9 codes were not changed during the time period of the study.

2.4 | ED disposition

The following ED disposition outcomes and their revenue codes were identified in our cohort: ED discharge, observation (0760 and 0761 and CPT codes 99217-99220, 99224-99226, and 99234-99236), inpatient admission (019x-016x), and intensive care unit (ICU) admission (020x and 021x). Observation admissions included patients who were admitted to an ED observation unit or were admitted to a hospital under observation status. ICU admissions included both ICU and coronary care unit admissions.

2.5 | Statistical analysis

Patient characteristics (age, sex, and census region) were described using median (inter-quartile range) or count (percentage), as appropriate. Annual rates were calculated using the number of ED visits for anaphylaxis as the numerator and total enrollees as the denominator. ED visit rates were expressed as number of ED visits for anaphylaxis per 100 000 enrollees. Linear regression analysis was performed to assess for trends by year in anaphylaxis ED visits (number of anaphylaxis ED visits per 100 000 enrollees).

Annual proportions were calculated using the number of outcomes as the numerator and total number of ED anaphylaxis visits as the denominator. We compared proportions across time using regression models (trend analysis). We calculated percentage change in proportions from 2005 to 2014 among anaphylaxis ED visits for ED discharge, observations, inpatient admission, and ICU admission by age-group and by trigger. The denominator for these calculations was the total number of visits for the specified age-group or trigger. Change in proportions was analyzed with the chi-square test. SAS software version 9.4 (SAS Institute Inc.) was used for all statistical analysis. All significance tests were 2-sided, and $P < .01$ was considered statistically significant.

Given the possibility of misreporting using method 2, which identifies patients through an algorithm of signs and symptoms based on the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria,¹² sensitivity analyses were planned a priori and included analysis of time trends among patients identified with method 1 only (ICD-9-CM diagnosis codes for anaphylaxis). Time trends among patients identified with method 1 were compared with trends obtained using both methods 1 and 2 to further validate our findings.

3 | RESULTS

3.1 | Characteristics of FIA ED visits

We identified 7310 ED visits for FIA in children younger than 18 years between January 1, 2005, and December 31, 2014

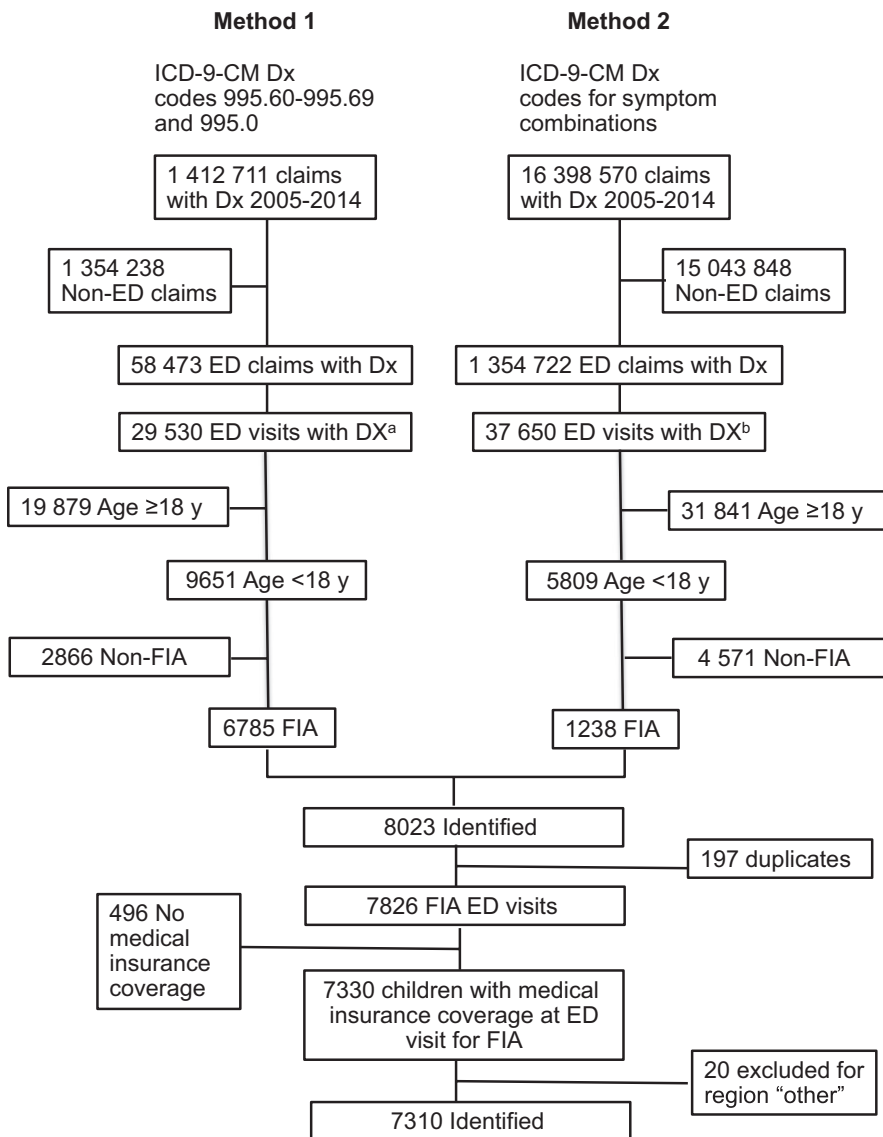


FIGURE 1 Flowchart of cohort identification. Dx indicates diagnosis; ED, emergency department; FIA, food-induced anaphylaxis; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification. ^aMore than 1 claim can be associated with a single ED visit; of the 58 473 claims, only 29 530 represented unique visits. ^bMore than 1 claim can be associated with a single ED visit; of the 1 354 722 claims, only 37 650 represented unique visits. (Adapted from Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Increasing emergency department visits for anaphylaxis, 2005-2014. *J Allergy Clin Immunol Pract.* 2017 Jan-Feb;5(1):171-175. Epub 2016 Nov 3. Used with permission)

(Figure 1). Overall, 60% of the patients were male (Table S1). The distribution by sex (male, 62.3% in 2005 to 60.2% in 2014; $P = .11$) and proportion of patients with a diagnosis of eczema (29.0% in 2005 to 27.7% in 2014; $P = .44$) and asthma (31.8% in 2005 to 31.3% in 2014; $P = .23$) remained constant during the 10-year study period. ED visit distribution by season appeared to be evenly distributed (Table S1).

3.2 | FIA ED visit rates and time trends

During the study time frame, ED visits for FIA in children increased by 214%, from 6.40 per 100 000 enrolled children in 2005 to 20.05 in 2014 ($P < .001$; Table 1). Infants and toddlers (0-2 years) had the highest rates of FIA-related ED visits (27.3 per 100 000 in 2014), followed by children aged 3-6 years (22.8 per 100 000 in 2014). Rates of FIA increased in all age-groups, with the highest rate of increase during the study period seen in adolescents aged 13-17 years (413%;

$P < .001$). Rates of FIA-related ED visits in children were highest among those in the Northeast US census region (44.9 per 100 000 enrollees in 2014).

3.3 | FIA ED visit trigger-specific rates and time trends

Overall, among specific food triggers, peanuts accounted for the highest rates of FIA-related ED visits (5.85 per 100 000 in 2014), followed by tree nuts/seeds (4.62 per 100 000 in 2014; Figure 2). The greatest increase was with tree nuts/seeds (373.0% increase over the study period; Table 1). Peanuts and tree nuts/seeds accounted for the largest rates of FIA-related ED visits and increased significantly during the study period for all age-groups (Table S2). Rates of milk and egg FIA-related ED visits increased significantly in younger pediatric patients (0-2 years) and did not significantly change in older pediatric patients (7-12 and 13-17 years; Table S2).

TABLE 1 Pediatric FIA ED visit rates and dispositions, 2005-2014

Feature	ED visits by year ^a										P value	% Change
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014		
Total Pediatric anaphylaxis-related ED visits	13.61	14.41	17.45	18.78	20.88	23.76	28.97	34.27	37.06	37.15	<.001	173.0%
All ED FIA visits	6.40	7.28	7.78	9.10	11.07	11.40	15.73	17.98	20.63	20.05	<.001	213.5%
Age, y												
0-2	11.05	14.12	14.65	18.98	19.57	19.43	24.09	25.18	29.94	27.31	<.001	147.1%
3-6	9.08	11.54	11.40	12.66	15.44	17.34	22.09	25.06	29.11	22.80	<.001	151.0%
7-12	4.88	4.04	4.09	5.13	7.26	7.45	11.55	13.18	15.39	16.15	<.001	230.9%
13-17	3.76	4.35	5.90	6.09	8.17	7.87	12.09	15.12	16.37	19.26	<.001	412.8%
Sex												
Female	4.93	5.38	6.29	7.21	9.23	8.74	14.08	15.41	16.50	16.29	<.001	230.5%
Male	7.80	9.09	9.21	10.92	12.83	13.96	17.31	20.46	24.59	23.67	<.001	203.5%
Trigger												
Peanut	1.99	2.50	2.61	3.21	3.65	3.59	5.30	5.77	6.72	5.85	<.001	194.6%
Shellfish/fish	0.52	0.40	0.47	0.50	0.72	0.52	0.78	0.87	0.83	0.87	.001	66.9%
Tree nuts/seeds	0.98	1.16	1.13	1.23	2.21	2.29	3.52	3.68	4.33	4.62	<.001	373.0%
Milk	0.42	0.36	0.56	0.66	0.58	0.74	1.02	1.05	1.19	1.07	<.001	152.5%
Egg	0.18	0.27	0.29	0.29	0.27	0.26	0.45	0.65	0.83	0.76	<.001	324.9%
Other ^b	1.06	1.13	1.19	1.46	2.09	2.12	2.30	3.09	3.99	3.79	<.001	257.8%
Unspecified	1.73	2.17	2.48	2.82	3.26	3.46	4.68	5.44	5.69	5.49	<.001	218.1%
Census region												
Midwest	7.24	7.58	8.43	9.45	13.48	13.42	18.50	21.59	25.90	23.21	<.001	220.6%
Northeast	20.25	16.70	20.29	22.73	24.76	25.44	33.43	40.51	45.66	44.91	<.001	121.8%
South	5.78	7.49	7.64	7.90	9.76	9.65	12.70	13.67	15.72	15.44	<.001	167.1%
West	7.47	10.75	9.16	13.77	13.32	14.49	21.51	23.20	23.25	23.20	<.001	210.6%
ED disposition ^c												
ED discharge	84.0	80.6	75.8	80.1	75.6	78.0	76.8	78.6	80.2	79.7	.48	-5.1%
Observation	9.7	10.9	15.7	13.3	17.9	15.8	18.6	17.7	15.5	16.8	.016	73.2%
Inpatient/ICU admission	6.4	8.5	8.5	6.6	6.5	6.2	4.6	3.8	4.3	3.5	.001	-45.3%

ED, emergency department; FIA, food-induced anaphylaxis; ICU, intensive care unit.

^aValues are No. of visits per 100 000 enrollees younger than 18 y unless noted otherwise.

^bOther includes fruit/vegetable.

^cValues are percentage of FIA-related ED visits among patients younger than 18 y.

3.4 | FIA ED visit patient observation and hospital admissions

Of the patients seen in the ED, most (78.8%) were discharged home directly from the ED (Table S1). Proportions of ED discharges and observations per FIA ED visits did not significantly change over the study time frame (Table 1). Observations accounted for 15.8% of all FIA ED visits studied (Table S1). Proportions of patients who observed appeared to be increasing among FIA ED visits, but the trend was not statistically significant (73%; $P = .016$; Table 1). Inpatient and ICU admissions

accounted for a minority of patients, and proportions significantly decreased over the study period (-45.3% change; $P = .001$; Table 1).

3.5 | Sensitivity analysis

A sensitivity analysis of only patients identified with method 1, including patients with ICD-9-CM diagnosis codes for anaphylactic shock, showed similar trends to the rates found with both methods for all age-groups and outcomes (Table S3).

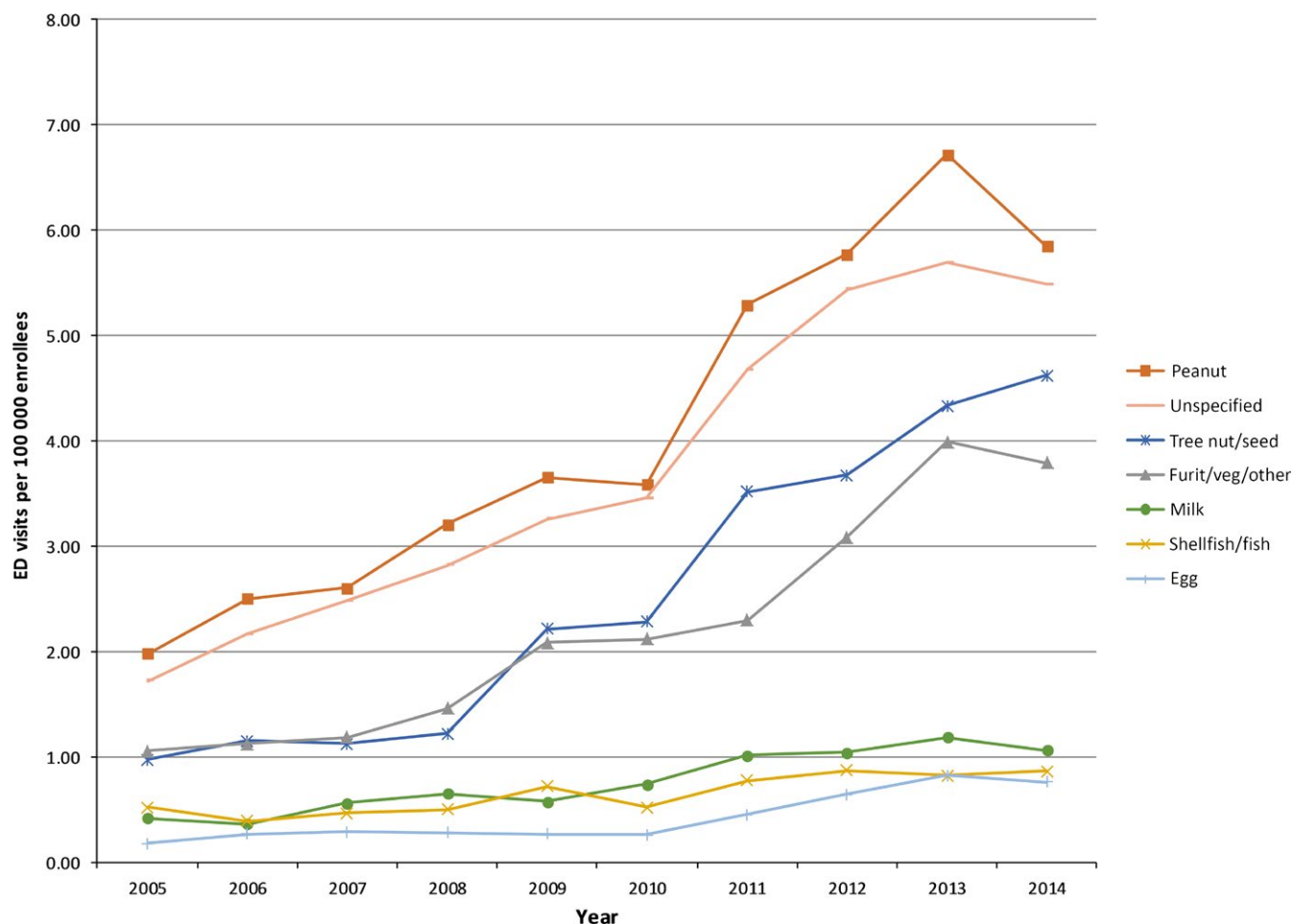


FIGURE 2 Pediatric food-induced anaphylaxis emergency department visit rates by trigger, 2005-2014 [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In this contemporary cohort study of 7310 FIA-related ED visits in children younger than 18 years, the most frequent ED visits were among children younger than 3 years, followed by 3- to 6-year-olds. Over the 10-year study time frame, ED visits for pediatric FIA increased four-fold in adolescents aged 13-17 years (413%). Among specified foods, peanuts accounted for the highest rates of FIA-related ED visits, followed by tree nuts/seeds. To our knowledge, this is one of the first studies to provide a comprehensive analysis of FIA-related ED visits in US children by analyzing specific triggers and healthcare utilization outcomes among children in multiple age-groups.

We found increasing rates of FIA ED visits, in contrast to a study by Clark et al,¹³ who reported stable trends from 2000 to 2009. However, our findings agree with more recent data citing increases in FIA-related ED visits.¹⁴ Given that our study concerned rates from 2005 to 2014, the increase in FIA-related ED visits most likely represents a relatively recent change. The increasing rates of ED visits related to FIA may be due to a combination of factors, including an increasing prevalence of food allergy, an increased awareness of the diagnosis, and a lower threshold for seeking acute medical care.¹⁵

In our cohort, whereas rates of FIA-related ED visits increased, overall proportions of inpatient and ICU admissions decreased. In a recently published study, Parlaman et al¹⁶ conducted a retrospective cohort study from 37 children's hospitals from 2007 to 2012 and similarly did not find any increase in the proportion of ED patients hospitalized or admitted to the ICU despite increasing rates of FIA-related ED visits. These findings suggest that most pediatric FIA ED cases are self-limited and do not require routine hospital admission. This agrees with guidelines that advise the observation period be individualized on the basis of factors that include reaction severity, access to care, and patient reliability.¹⁷ Future studies examining FIA-related ED outcomes are necessary to ensure proper healthcare delivery.

The decrease in proportions of inpatient and ICU admissions is likely due to increased utilization of ED observation units or inpatient observation status. In their study, Parlaman et al¹⁶ did not examine rates of patients sent to observation units. Although not specifically demonstrated in that study, the important role of observation units in managing anaphylaxis has been highlighted in other studies. In a study in an Australian pediatric ED, Braganza et al¹⁸ reported results similar to ours: 39% of children were observed in an observation unit, compared with 7% who were admitted to a general

medical unit. Use of observation units can decrease hospital costs by reducing inpatient admissions,¹⁹ and they are fitting venues for most patients seen in the ED for anaphylaxis, which is often self-limited. Approximately 36% of US EDs reported having observation units in 2007,²⁰ so implementing ED observation unit protocols to facilitate the care of anaphylaxis patients, as described by Manivannan et al,²¹ may be helpful.

Cow's milk and egg triggers were more common among the very young (0-2 years) compared with older preschool- and school-aged patients (≥ 3 years). Our findings are similar to those of a study based on the European Anaphylaxis Registry, which found that cow's milk and egg triggers were more common in those younger than 6 years.²² These findings are most likely related to the common changes in dietary habits of children. In our study, peanut was a common trigger for anaphylaxis for all age-groups, and this was similar to the findings from the European Anaphylaxis Registry study.²² However, this was not true in Spain, where a study examining pediatric anaphylaxis in the ED reported that milk was the most common food trigger.²³ In our cohort, tree nuts were a common trigger for anaphylaxis across all age-groups and increased the most over the 10-year study period. In the European Anaphylaxis Registry study,²² reactions to tree nuts (specifically cashew and hazelnut) occurred most commonly in preschool-aged children (< 6 years) and were less frequent in older children (6-12 years) and adolescents (13-17 years). Cross-cultural differences in feeding practices may explain these differences, and additional studies are needed to further define the effects of culture and environment on the development of food allergies.

Infants and toddlers (0-2 years) had the highest rates of anaphylaxis-related ED visits. This is similar to results published from a single pediatric ED study from Spain who reported the highest incidence occurred in patients younger than 12 months, particularly those aged 6-12 months.²³ Specific reasons for these trends are unclear, and additional studies are needed to further explore these findings.

In our study, the rates of anaphylaxis ED visits increased fourfold among adolescents aged 13-17 years. Adolescents have the highest risk of fatal anaphylaxis, which has been attributed to increased risk-taking behavior with eating, not carrying an EAI, and denial of their allergies.²⁴ A multidimensional approach that incorporates social networks into management strategies and promotes patient education and guideline adherence, including carrying an EAI, will be important in overcoming barriers in this patient population.²⁵

Rates of FIA-related ED visits in children were highest among those in the Northeast, similar to previous studies. Studies from the United States²⁶ and Australia²⁷ have reported higher incidence of pediatric emergency visits and hospitalizations for anaphylaxis, along with higher rates of EAI prescriptions, in areas with less sunlight. Decreased sunlight exposure has been associated with decreased vitamin D,²⁶ which may be a protective factor. FIA rates remained constant during the seasons, most likely because food allergens are available year-round, in contrast to some venoms, insects, or aeroallergens.

Our study has several potential limitations. We used administrative claims, which are susceptible to coding errors, such as

undercoding comorbid conditions or outcomes. To mitigate this limitation, we included only patients enrolled in an insurance plan for at least 30 days before the ED visit. We also did not evaluate the cost of interventions, nor were we able to evaluate the time spent in the ED or if the observation was performed in an ED observation unit or on a hospital unit. We were able to estimate hospitalizations as markers of healthcare utilization and indirect markers of healthcare cost. Finally, our sample is large and diverse in age and geographic representation, but it is not a true national sample and is limited to privately insured and Medicare Advantage enrollees. As such, our findings may not easily generalize to Medicaid, Medicare fee-for-service, or uninsured populations.

The strengths of our study are the use of "real-world" data outside clinical trials and a large sample that included both academic and non-academic institutions across the United States. In addition, we used rigorous methods to select the study population and rigorous data analysis to measure healthcare utilization. Furthermore, our sensitivity analysis demonstrated similar trends when a more specific method of anaphylaxis recognition was used, which suggests that our data represent true time trends.

Food-induced anaphylaxis represents an increasing public health burden associated with increasing rates of healthcare utilization. Awareness of these FIA trends by clinicians, patients, and the community is essential for preventing adverse outcomes. Encouraging partnerships among medical specialties including allergy/immunology, pediatrics, family medicine, and emergency medicine and the community is key to creating strategies for acute management of FIA and prevention of recurrence.

CONFLICT OF INTEREST

R. L. Campbell is a consultant for INSYS Therapeutics and an author for UpToDate.

AUTHOR CONTRIBUTIONS

R.L.C., M.S.M., and M.F.B. substantially contributed to the conception or design of the work or interpreted the data for the work; drafted the work and revised it critically for important intellectual content; approved the final version to be published; and prepared an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. H.K.V. substantially contributed to design of the work and the acquisition and analysis of data for the work; drafted the work and revised it critically for important intellectual content; approved the final version to be published; and prepared an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. N.D.S. substantially contributed to conception or design of the work and the acquisition, analysis, and interpretation of data for the work; revised the work critically for important intellectual content; approved the final version to be

published; and prepared an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACCESS TO DATA

H.K.V. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ROLE OF FUNDER/SPONSOR

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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REFERENCES

1. Sampson HA. Food anaphylaxis. *Br Med Bull*. 2000;56:925-935.
2. Wang J, Sampson HA. Food anaphylaxis. *Clin Exp Allergy*. 2007;37:651-660.
3. Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol*. 2015;135:956-963.
4. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med*. 2005;28:381-388.
5. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol*. 2009;123:434-442.
6. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief*. 2013;1-8.
7. Branum AM, Lukacs SL. Food allergy among US children: trends in prevalence and hospitalizations. *NCHS Data Brief*. 2008;1-8.
8. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum Labs: building a novel node in the learning health care system. *Health Aff (Millwood)*. 2014;33:1187-1194. Erratum in: *Health Aff (Millwood)*. 2014;33:1703.
9. Optum. Optum research data assets [Internet]. 2015;16. https://cdn-aem.optum.com/content/dam/optum3/optum/en/resources/guides/5302_Data_Assets_Chart_Sheet_ISPOR.pdf. Accessed November 17, 2016.
10. Benchimol EI, Smeeth L, Guttman A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12:e1001885.
11. Harduar-Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. *J Allergy Clin Immunol*. 2010;126:98-104.
12. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol*. 2006;97:596-602.
13. Clark S, Espinola JA, Rudders SA, Banerji A, Camargo CA. Favorable trends in the frequency of US emergency department visits for food allergy, 2001-2009. *Allergy Asthma Proc*. 2013;34:439-445.
14. Rudders SA, Arias SA, Camargo CA Jr. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000-2009. *J Allergy Clin Immunol*. 2014;134:960-962.e3.
15. Michelson KA, Monuteaux MC, Neuman MI. Variation and trends in anaphylaxis care in United States children's hospitals. *Acad Emerg Med*. 2016;23:623-627.
16. Parlaman JP, Oron AP, Uspal NG, DeJong KN, Tieder JS. Emergency and hospital care for food-related anaphylaxis in children. *Hosp Pediatr*. 2016;6:269-274.
17. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med*. 2006;47:373-380.
18. Braganza SC, Acworth JP, Mckinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child*. 2006;91:159-163.
19. Baugh CW, Venkatesh AK, Bohan JS. Emergency department observation units: a clinical and financial benefit for hospitals. *Health Care Manage Rev*. 2011;36:28-37.
20. Hess EP, Nestler DM. Transforming the emergency department observation unit: a look into the future. *Cardiol Clin*. 2012;30:501-521.
21. Manivannan V, Hess EP, Bellamkonda VR, et al. A multifaceted intervention for patients with anaphylaxis increases epinephrine use in adult emergency department. *J Allergy Clin Immunol Pract*. 2014;2:294-299.e1.
22. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: the European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016;137:1128-1137.e1. Epub 2016 Jan 21.
23. Alvarez-Perea A, Ameiro B, Morales C, et al. Anaphylaxis in the pediatric emergency department: analysis of 133 cases after an allergy workup. *J Allergy Clin Immunol Pract*. 2017;5:1256-1263.
24. Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy Clin Immunol*. 2006;117:1440-1445.
25. Nwaru BI, Sheikh A. Anaphylaxis in adolescents: a potential tripartite management framework. *Curr Opin Allergy Clin Immunol*. 2015;15:344-349.
26. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol*. 2007;120:131-136.
27. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in epinephrine autoinjector prescriptions in Australia: more evidence for the vitamin D-anaphylaxis hypothesis. *Ann Allergy Asthma Immunol*. 2009;103:488-495.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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National Trends in Emergency Department Visits and Hospitalizations for Food-Induced Anaphylaxis in US Children

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~~Motosue MS, Bellolio M.F., Van Houten HK, Shah ND, and Campbell RL.~~

~~National Trends in Emergency Department Visits and Hospitalizations for Food-Induced Anaphylaxis in US Children~~

~~Pediatr Allergy Immunol.~~

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Abstract

~~**Background:** Food is the leading cause of anaphylaxis in children seen in emergency departments in the United States, yet data on emergency department visits and hospitalizations related to food-induced anaphylaxis are limited. The objective of our study was to examine national time trends of pediatric food-induced anaphylaxis-related emergency department visits and hospitalizations.~~

~~**Methods:** We conducted an observational study using a national administrative claims database from 2005 through 2014. Participants were younger than 18 years with an emergency department visit or hospitalization for food-induced anaphylaxis. Outcome measures of our study included time trends of pediatric food-induced anaphylaxis-related emergency department visits and hospitalizations, including observations (in an emergency department or a hospital unit), inpatient admissions, and intensive care unit admissions.~~

~~**Results:** During the study period, participants had 7,310 food-induced anaphylaxis-related emergency department visits. Emergency department visits for food-induced anaphylaxis increased by 214% ($P<.001$); the highest rates were in infants and toddlers~~

(age 0-2 years). Rates of emergency department visits significantly increased in all age groups, with the highest increase in adolescents (age 13-17 years: 413%; $P<.001$). Peanuts accounted for the highest rates (5.85 per 100,000 in 2014) followed by tree nuts/seeds (4.62 per 100,000 in 2014). The greatest increase in rates of emergency department visits for food-induced anaphylaxis occurred with tree nuts/seeds (373.0% increase during the study period).

Conclusions: The incidence of food-induced anaphylaxis has significantly increased over time in children of all ages. Food-induced anaphylaxis in children is an important national public health concern.

Keywords: children; epidemiology; food-induced anaphylaxis

Abbreviations

EAI, epinephrine autoinjector

ED, emergency department

FIA, food-induced anaphylaxis

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification

ICU, intensive care unit

US, United States

Introduction

Food-induced anaphylaxis (FIA) is the leading cause of anaphylaxis treated in emergency departments (EDs) in the United States (US) (1). FIA refers to a potentially fatal hypersensitivity reaction to ingested foods. FIA accounts for 30% to 50% of anaphylaxis cases in the US (2), in other developed countries in Europe (3), Asia (4), and in Australia (5).

According to the Centers for Disease Control and Prevention, rates of food allergies in US children increased by about 50% between 1997 and 2011 (6). Furthermore, the Centers for Disease Control and Prevention reported that approximately 10,000 children were hospitalized in the US from 2004 to 2006 with a diagnosis of food allergy (7). This number was 3 times higher than previous estimates from 1998.

Comprehensive studies examining time trends are important for improving public awareness and directing public health initiatives to reduce morbidity and mortality. The objective of this study was to examine contemporary time trends related to ED visits and hospitalizations for FIA to better understand and characterize the burden of FIA in US children.

Methods

Data Source

This observational study used the OptumLabs Data Warehouse, which includes administrative claims data for more than 100 million privately insured and Medicare Advantage enrollees (8). The database contains longitudinal health information from geographically diverse regions across the US spanning more than 20 years. The data cover multiple domains, including enrollee information (sex, age, race/ethnicity, dates of eligibility, census region) and medical claims (including International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes) (9). This study was deemed exempt from institutional review board approval because it involved

analysis of pre-existing, deidentified data. The study followed standardized reporting guidelines (RECORD: REporting of studies Conducted using Observational Routinely-collected health Data) (10).

Study Population

—————Children younger than 18 years were included in this study. To identify the cohort of ED anaphylaxis visits from 2005 to 2014, we used 2 previously validated methods (11). Method 1 identified patients with ICD-9-CM anaphylactic shock diagnosis codes (995.60-995.69 and 995.0). Method 2 identified patients through a validated algorithm of ICD-9-CM codes of symptom combinations (11). At least 30 days of medical insurance coverage before the ED visit was required for inclusion in the study cohort. Similarly, medical insurance coverage for at least 30 days in the given calendar year was required for ED visits included in the denominator for rate calculations. ED visits identified by both methods were combined; duplicate visits were excluded.

Food Triggers

—————Specific food triggers were identified by the following associated ICD-9-CM codes: cow's milk (995.67), egg (995.68), peanuts (995.61), tree nuts and seeds (995.64), crustaceans (995.62), fish (995.65), and other (995.69) which included fruits and vegetables (995.63). The ICD-9 codes were not changed during the time period of the study.

ED Disposition

—————The following ED disposition outcomes and their revenue codes were identified in our cohort: ED discharge, observation (0760 and 0761 and CPT codes 99217-99220, 99224-99226, and 99234-99236), inpatient admission (019x-016x), and intensive care unit (ICU) admission (020x and 021x). Observation admissions included patients who were admitted to an ED observation unit or were admitted to a hospital

under observation status. ICU admissions included both ICU and coronary care unit admissions.

Statistical Analysis

————— Patient characteristics (age, sex, census region) were described using median (interquartile range) or count (percentage), as appropriate. Annual rates were calculated by using the number of ED visits for anaphylaxis as the numerator and total enrollees as the denominator. ED visit rates were expressed as number of ED visits for anaphylaxis per 100,000 enrollees. Linear regression analysis was performed to assess for trends by year in anaphylaxis ED visits (number of anaphylaxis ED visits per 100,000 enrollees).

————— Annual proportions were calculated by using the number of outcomes as the numerator and total number of ED anaphylaxis visits as the denominator. We compared proportions across time using regression models (trend analysis). We calculated percentage change in proportions from 2005 to 2014 among anaphylaxis ED visits for ED discharge, observations, inpatient admission, and ICU admission by age group and by trigger. The denominator for these calculations was the total number of visits for the specified age group or trigger. Change in proportions was analyzed with the χ^2 test. SAS software version 9.4 (SAS Institute Inc.) was used for all statistical analysis. All significance tests were 2-sided, and $P < .01$ was considered statistically significant.

————— Given the possibility of misreporting using method 2, which identifies patients through an algorithm of signs and symptoms based on the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria (12), sensitivity analyses were planned a priori and included analysis of time trends among patients identified with method 1 only (ICD-9-CM diagnosis codes for anaphylaxis). Time trends among patients identified with method 1 were compared with trends obtained using both methods 1 and 2 to further validate our findings.

Results

Characteristics of FIA ED Visits

————— We identified 7,310 ED visits for FIA in children younger than 18 years between January 1, 2005, and December 31, 2014 (Figure 1). Overall, 60% of the patients were male (Supplemental Table 1). The distribution by sex (male, 62.3% in 2005 to 60.2% in 2014; $P=.11$) and proportion of patients with a diagnosis of eczema (29.0% in 2005 to 27.7% in 2014; $P=.44$) and asthma (31.8% in 2005 to 31.3% in 2014; $P=.23$) remained constant during the 10-year study period. ED visit distribution by season appeared to be evenly distributed (Supplemental Table 1).

FIA ED Visit Rates and Time Trends

————— During the study time frame, ED visits for FIA in children increased by 214%, from 6.40 per 100,000 enrolled children in 2005 to 20.05 in 2014 ($P<.001$) (Table). Infants and toddlers (0-2 years) had the highest rates of FIA-related ED visits (27.3 per 100,000 in 2014), followed by children aged 3 to 6 years (22.8 per 100,000 in 2014). Rates of FIA increased in all age groups, with the highest rate of increase during the study period seen in adolescents aged 13 to 17 years (413%; $P<.001$). Rates of FIA-related ED visits in children were highest among those in the Northeast US census region (44.9 per 100,000 enrollees in 2014).

FIA ED Visit Trigger-Specific Rates and Time Trends

————— Overall, among specific food triggers, peanuts accounted for the highest rates of FIA-related ED visits (5.85 per 100,000 in 2014), followed by tree nuts/seeds (4.62 per 100,000 in 2014) (Figure 2). The greatest increase was with tree nuts/seeds (373.0% increase over the study period) (Table). Peanuts and tree nuts/seeds accounted for the largest rates of FIA-related ED visits and increased significantly during the study period for all age groups (Supplemental Table 2). Rates of milk and egg FIA-related ED visits

increased significantly in younger pediatric patients (0-2 years) and did not significantly change in older pediatric patients (7-12 years and 13-17 years) (Supplemental Table 2).

FIA ED Visit Patient Observation and Hospital Admissions

Of the patients seen in the ED, most (78.8%) were discharged home directly from the ED (Supplemental Table 1). Proportions of ED discharges and observations per FIA ED visits did not significantly change over the study time frame (Table).

Observations accounted for 15.8% of all FIA ED visits studied (Supplemental Table 1).

Proportions of patients who were observed appeared to be increasing among FIA ED visits, but the trend was not statistically significant (73%; $P=.016$) (Table). Inpatient and ICU admissions accounted for a minority of patients and proportions significantly decreased over the study period (–45.3% change; $P=0.001$) (Table).

Sensitivity Analysis

A sensitivity analysis of only patients identified with method 1, including patients with ICD-9-CM diagnosis codes for anaphylactic shock, showed similar trends to the rates found with both methods for all age groups and outcomes (Supplemental Table 3).

Discussion

In this contemporary cohort study of 7,310 FIA-related ED visits in children younger than 18 years, the most frequent ED visits were among children younger than 3 years, followed by 3- to 6-year-olds. Over the 10-year study time frame, ED visits for pediatric FIA increased 4 fold in adolescents aged 13 to 17 years (413%). Among specified foods, peanuts accounted for the highest rates of FIA-related ED visits, followed by tree nuts/seeds. To our knowledge, this is one of the first studies to provide a comprehensive analysis of FIA-related ED visits in US children by analyzing specific triggers and health care utilization outcomes among children in multiple age groups.

—————We found increasing rates of FIA ED visits, in contrast to a study by Clark et al (13), who reported stable trends from 2000 to 2009. However, our findings agree with more recent data citing increases in FIA-related ED visits (14). Given that our study concerned rates from 2005 to 2014, the increase in FIA-related ED visits most likely represents a relatively recent change. The increasing rates of ED visits related to FIA may be due to a combination of factors, including an increasing prevalence of food allergy, an increased awareness of the diagnosis, and a lower threshold for seeking acute medical care (15).

—————In our cohort, whereas rates of FIA-related ED visits increased, overall proportions of inpatient and ICU admissions decreased. In a recently published study, Parlaman et al (16) conducted a retrospective cohort study from 37 children's hospitals from 2007 to 2012 and similarly did not find any increase in the proportion of ED patients hospitalized or admitted to the ICU despite increasing rates of FIA-related ED visits. These findings suggest that most pediatric FIA ED cases are self-limited and do not require routine hospital admission. This agrees with guidelines that advise the observation period be individualized on the basis of factors that include reaction severity, access to care, and patient reliability (17). Future studies examining FIA-related ED outcomes are necessary to ensure proper health care delivery.

—————The decrease in proportions of inpatient and ICU admissions is likely due increased utilization of ED observation units or inpatient observation status. In their study, Parlaman et al (16) did not examine rates of patients sent to observation units. Although not specifically demonstrated in that study, the important role of observation units in managing anaphylaxis has been highlighted in other studies. In a study in an Australian pediatric ED, Braganza et al (18) reported results similar to ours: 39% of children were observed in an observation unit, compared with 7% who were admitted to a general medical unit. Use of observation units can decrease hospital costs by reducing

inpatient admissions (19), and they are fitting venues for most patients seen in the ED for anaphylaxis, which is often self-limited. Approximately 36% of US EDs reported having observation units in 2007 (20), so implementing ED observation unit protocols to facilitate the care of anaphylaxis patients, as described by Manivannan et al (21), may be helpful.

————— Cow's milk and egg triggers were more common among the very young (0–2 years) compared with older preschool and school-aged patients (≥ 3 years). Our findings are similar to those of a study based on the European Anaphylaxis Registry, which found that cow's milk and egg triggers were more common in those younger than 6 years (22). These findings are most likely related to the common changes in dietary habits of children. In our study, peanut was a common trigger for anaphylaxis for all age groups, and this was similar to the findings from the European Anaphylaxis Registry study (22). However, this was not true in Spain, where a study examining pediatric anaphylaxis in the ED reported that milk was the most common food trigger (23). In our cohort, tree nuts were a common trigger for anaphylaxis across all age groups and increased the most over the 10-year study period. In the European Anaphylaxis Registry study (22), reactions to tree nuts (specifically cashew and hazelnut) occurred most commonly in preschool-aged children (< 6 years) and were less frequent in older children (6–12 years) and adolescents (13–17 years). Cross-cultural differences in feeding practices may explain these differences and additional studies are needed to further define the effects of culture and environment on the development of food allergies.

————— Infants and toddlers (0–2 years) had the highest rates of anaphylaxis-related ED visits. This is similar to results published from a single pediatric ED study from Spain who reported the highest incidence occurred in patients younger than 12 months, particularly those aged 6 to 12 months (23). Specific reasons for these trends are unclear and additional studies are needed to further explore these findings.

————— In our study, the rates of anaphylaxis ED visits increased 4 fold among adolescents aged 13 to 17 years. Adolescents have the highest risk of fatal anaphylaxis, which has been attributed to increased risk taking behavior with eating, not carrying an EAI, and denial of their allergies (24). A multidimensional approach that incorporates social networks into management strategies and promotes patient education and guideline adherence, including carrying an EAI, will be important in overcoming barriers in this patient population (25).

————— Rates of FIA related ED visits in children were highest among those in the Northeast, similar to previous studies. Studies from the US (26) and Australia (27), have reported higher incidence of pediatric emergency visits and hospitalizations for anaphylaxis, along with higher rates of EAI prescriptions, in areas with less sunlight. Decreased sunlight exposure has been associated with decreased vitamin D (26), which may be a protective factor. FIA rates remained constant during the seasons, most likely because food allergens are available year round, in contrast to some venoms, insects, or aeroallergens.

————— Our study has several potential limitations. We used administrative claims, which are susceptible to coding errors, such as undercoding comorbid conditions or outcomes. To mitigate this limitation, we included only patients enrolled in an insurance plan for at least 30 days before the ED visit. We also did not evaluate the cost of interventions, nor were we able to evaluate the time spent in the ED or if the observation was performed in an ED observation unit or on a hospital unit. We were able to estimate hospitalizations as markers of health care utilization and indirect markers of health care cost. Finally, our sample is large and diverse in age and geographic representation, but it is not a true national sample and is limited to privately insured and Medicare Advantage enrollees. As such, our findings may not easily generalize to Medicaid, Medicare fee for service, or uninsured populations.

—————The strengths of our study are the use of “real-world” data outside clinical trials and a large sample that included both academic and nonacademic institutions across the US. In addition, we used rigorous methods to select the study population and rigorous data analysis to measure health care utilization. Furthermore, our sensitivity analysis demonstrated similar trends when a more specific method of anaphylaxis recognition was used, which suggests that our data represent true time trends.

—————FIA represents an increasing public health burden associated with increasing rates of health care utilization. Awareness of these FIA trends by clinicians, patients, and the community is essential for preventing adverse outcomes. Encouraging partnerships among medical specialties including allergy/immunology, pediatrics, family medicine, and emergency medicine and the community is key to creating strategies for acute management of FIA and prevention of recurrence.

Acknowledgments

Author Contributions:

R.L.C., M.S.M., and M.F.B.: 1) substantial contributions to conception or design of the work, or interpretation of data for the work; 2) drafting of the work and revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

H.K.V.: 1) substantial contributions to design of the work and the acquisition and analysis of data for the work; 2) drafting of the work and revising it critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

N.D.S.: 1) substantial contributions to conception or design of the work and the acquisition, analysis, and interpretation of data for the work; 2) revising the work critically for important intellectual content; 3) final approval of the version to be published; and 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Access to Data:

H.K.V.: had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Potential Conflicts of Interest: None.

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Additional Information: None.

References

1. Sampson HA. Food anaphylaxis. *Br Med Bull.* 2000;56(4):925-35.
2. Wang J, Sampson HA. Food anaphylaxis. *Clin Exp Allergy.* 2007 May;37(5):651-60.
3. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol.* 2015 Apr;135(4):956-63.
4. Smit DV, Cameron PA, Rainer TH. Anaphylaxis presentations to an emergency department in Hong Kong: incidence and predictors of biphasic reactions. *J Emerg Med.* 2005 May;28(4):381-8.
5. Liew WK, Williamson E, Tang ML. Anaphylaxis fatalities and admissions in Australia. *J Allergy Clin Immunol.* 2009 Feb;123(2):434-42.
6. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief.* 2013 May;(121):1-8.
7. Branum AM, Lukacs SL. Food allergy among US children: trends in prevalence and hospitalizations. *NCHS Data Brief.* 2008 Oct;(10):1-8.
8. Wallace PJ, Shah ND, Dennen T, Bleicher PA, Crown WH. Optum Labs: building a novel node in the learning health care system. *Health Aff (Millwood).* 2014 Jul;33(7):1187-94. Erratum in: *Health Aff (Millwood).* 2014 Sep;33(9):1703.
9. Optum. Optum research data assets [Internet]. 2015 Jun 15 [cited 2016 Nov 17]; [16 p.] Available from: https://cdn-aem.optum.com/content/dam/optum3/optum/en/resources/guides/5302_Data_Assets_Chart_Sheet_ISPOR.pdf.
10. Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, et al; RECORD Working Committee. The REporting of studies Conducted using Observational

Routinely collected health Data (RECORD) statement. PLoS Med. 2015 Oct 6;12(10):e1001885.

11. Harduar Morano L, Simon MR, Watkins S, Blackmore C. Algorithm for the diagnosis of anaphylaxis and its validation using population-based data on emergency department visits for anaphylaxis in Florida. J Allergy Clin Immunol. 2010 Jul;126(1):98-104.

12. Lieberman P, Camargo CA Jr, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. Ann Allergy Asthma Immunol. 2006 Nov;97(5):596-602.

13. Clark S, Espinola JA, Rudders SA, Banerji A, Camargo CA. Favorable trends in the frequency of US emergency department visits for food allergy, 2001-2009. Allergy Asthma Proc. 2013 Sep-Oct;34(5):439-45.

14. Rudders SA, Arias SA, Camargo CA Jr. Trends in hospitalizations for food-induced anaphylaxis in US children, 2000-2009. J Allergy Clin Immunol. 2014 Oct;134(4):960-2.e3.

15. Michelson KA, Monuteaux MC, Neuman MI. Variation and trends in anaphylaxis care in United States children's hospitals. Acad Emerg Med. 2016 May;23(5):623-7.

16. Parlaman JP, Oron AP, Uspal NG, DeJong KN, Tieder JS. Emergency and hospital care for food-related anaphylaxis in children. Hosp Pediatr. 2016 May;6(5):269-74.

17. Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report: second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med. 2006 Apr;47(4):373-80.

18. Braganza SC, Acworth JP, McKinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child*. 2006 Feb;91(2):159-63.
19. Baugh CW, Venkatesh AK, Bohan JS. Emergency department observation units: a clinical and financial benefit for hospitals. *Health Care Manage Rev*. 2011 Jan-Mar;36(1):28-37.
20. Hess EP, Nestler DM. Transforming the emergency department observation unit: a look into the future. *Cardiol Clin*. 2012 Nov;30(4):501-21.
21. Manivannan V, Hess EP, Bellamkonda VR, Nestler DM, Bellolio MF, Hagan JB, et al. A multifaceted intervention for patients with anaphylaxis increases epinephrine use in adult emergency department. *J Allergy Clin Immunol Pract*. 2014 May-Jun;2(3):294-9.e1.
22. Grabenhenrich LB, Dolle S, Moneret-Vautrin A, Kohli A, Lange L, Spindler T, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016 Apr;137(4):1128-37.e1. Epub 2016 Jan 21.
23. Alvarez-Perea A, Ameiro B, Morales C, et al. Anaphylaxis in the Pediatric Emergency Department: Analysis of 133 Cases After an Allergy Workup. *J Allergy Clin Immunol Pract*. 2017;5(5):1256-1263.
24. Sampson MA, Munoz-Furlong A, Sicherer SH. Risk-taking and coping strategies of adolescents and young adults with food allergy. *J Allergy Clin Immunol*. 2006 Jun;117(6):1440-5.
25. Nwaru BI, Sheikh A. Anaphylaxis in adolescents: a potential tripartite management framework. *Curr Opin Allergy Clin Immunol*. 2015 Aug;15(4):344-9.
26. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol*. 2007 Jul;120(1):131-6.

~~27. Mullins RJ, Clark S, Camargo CA Jr. Regional variation in epinephrine autoinjector prescriptions in Australia: more evidence for the vitamin D-anaphylaxis hypothesis. Ann Allergy Asthma Immunol. 2009 Dec;103(6):488-95.~~

Table. Pediatric FIA-ED Visit Rates and Dispositions, 2005–2014

[illegible]

ED-discharge	84.0	80.6	75.8	80.1	75.6	78.0	76.8	78.6	80.2	79.7	0.48	-5.1%
Observation	9.7	10.9	15.7	13.3	17.9	15.8	18.6	17.7	15.5	16.8	0.016	73.2%
Inpatient/ICU-admission	6.4	8.5	8.5	6.6	6.5	6.2	4.6	3.8	4.3	3.5	0.001	-45.3%

Abbreviations: ED, emergency department; FIA, food-induced anaphylaxis; ICU, intensive care unit.

^a Values are No. of visits per 100,000 enrollees younger than 18 years unless noted otherwise.

^b Other includes fruit/vegetable.

^c Values are percentage of FIA-related ED-visits among patients younger than 18 years.

Legend

Figure 1. Flow chart of cohort identification. Dx indicates diagnosis; ED, emergency department; FIA, food-induced anaphylaxis; ICD-9 CM, International Classification of Diseases, 9th Revision, Clinical Modification.^a More than 1 claim can be associated with a single ED visit; of the 58,473 claims, only 29,530 represented unique visits.^b More than 1 claim can be associated with a single ED visit; of the 1,354,772 claims, only 37,650 represented unique visits. (Adapted from Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Increasing emergency department visits for anaphylaxis, 2005-2014. *J Allergy Clin Immunol Pract*. 2017 Jan-Feb;5(1):171-5. Epub 2016 Nov 3. Used with permission.)

Figure 2. Pediatric Food-Induced Anaphylaxis Emergency Department Visit Rates by Trigger, 2005-2014

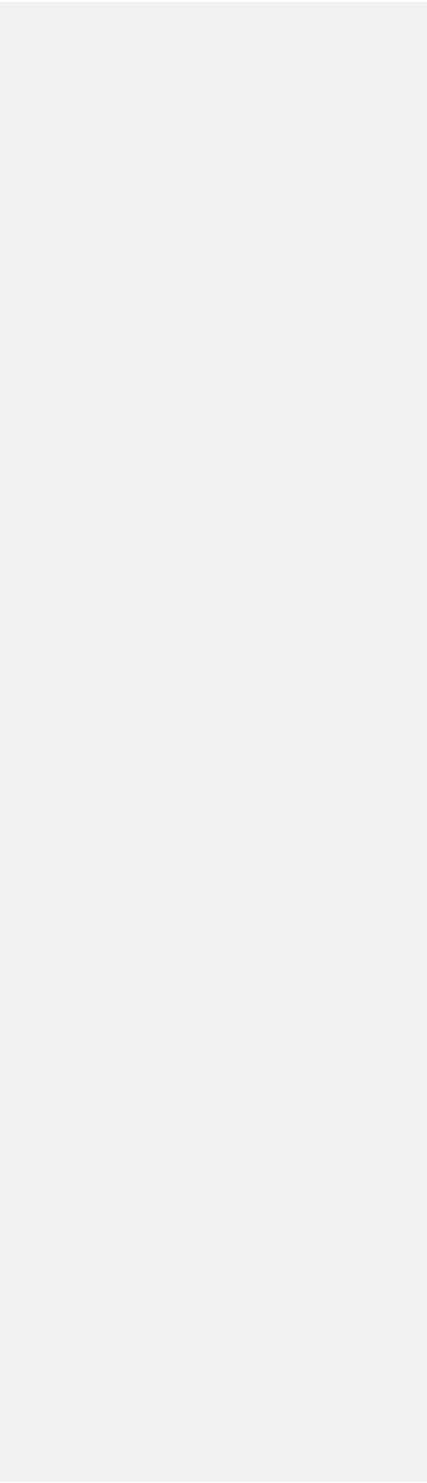
Supplemental Table 1. Characteristics of Children With FIA, 2005-2014^a

Characteristic	Year										Total (N=7310)
	2005 (N=393)	2006 (N=459)	2007 (N=483)	2008 (N=542)	2009 (N=615)	2010 (N=613)	2011 (N=867)	2012 (N=1031)	2013 (N=1200)	2014 (N=1107)	
Age at ED visit, y	5 (2-11)	4 (2-10)	5 (2-11)	4 (2-10)	6 (2-11)	5 (3-11)	6 (3-12)	7 (3-13)	6 (3-12)	8 (3-13)	6 (3-12)
Age, y											
0-2	103 (26.2)	134 (29.2)	136 (28.2)	168 (31.0)	157 (25.5)	148 (24.1)	186 (21.5)	202 (19.6)	244 (20.3)	211 (19.1)	1689 (23.1)
3-6	121 (30.8)	158 (34.4)	153 (31.7)	163 (30.1)	185 (30.1)	201 (32.8)	261 (30.1)	307 (29.8)	358 (29.8)	264 (23.8)	2171 (29.7)
7-12	101 (25.7)	86 (18.7)	86 (17.8)	104 (19.2)	138 (22.4)	138 (22.5)	220 (25.4)	261 (25.3)	309 (25.8)	309 (27.9)	1752 (24.0)
13-17	68 (17.3)	81 (17.6)	108 (22.4)	107 (19.7)	135 (22.0)	126 (20.6)	200 (23.1)	261 (25.3)	289 (24.1)	323 (29.2)	1698 (23.2)
Male sex	245 (62.3)	293 (63.8)	292 (60.5)	332 (61.3)	364 (59.2)	383 (62.5)	487 (56.2)	598 (58.0)	729 (60.8)	666 (60.2)	4389 (60.0)
Census region											
Midwest	106 (27.0)	111 (24.2)	119 (24.6)	130 (24.0)	173 (28.1)	170 (27.7)	241 (27.8)	296 (28.7%)	362 (30.2%)	311 (28.1%)	2019 (27.6)
Northeast	101 (25.7)	87 (19.0)	109 (22.6)	120 (22.1)	124 (20.2)	127 (20.7)	179 (20.6)	225 (21.8)	263 (21.9)	252 (22.8)	1587 (21.7)

Motosue et al -25- (ABQ)											
South	132 (33.6)	179 (39.0)	185 (38.3)	187 (34.5)	219 (35.6)	209 (34.1)	285 (32.9)	324 (31.4)	375 (31.3)	344 (31.1)	2439 (33.4)
West	54 (13.7)	82 (17.9)	70 (14.5)	105 (19.4)	99 (16.1)	107 (17.5)	162 (18.7)	186 (18.0)	200 (16.7)	200 (18.1)	1265 (17.3)
Eczema	114 (29.0)	113 (24.6)	117 (24.2)	134 (24.7)	196 (31.9)	161 (26.3)	259 (29.9)	290 (28.1)	329 (27.4)	307 (27.7)	2020 (27.6)
Asthma	125 (31.8)	136 (29.6)	131 (27.1)	180 (33.2)	186 (30.2)	204 (33.3)	287 (33.1)	334 (32.4)	391 (32.6)	346 (31.3)	2320 (31.7)
ED disposition											
ED discharge	330 (84.0)	370 (80.6)	366 (75.8)	434 (80.1)	465 (75.6)	478 (78.0)	666 (76.8)	810 (78.6)	962 (80.2)	882 (79.7)	5763 (78.8)
Observation	38 (9.7)	50 (10.9)	76 (15.7)	72 (13.3)	110 (17.9)	97 (15.8)	161 (18.6)	182 (17.7)	186 (15.5)	186 (16.8)	1158 (15.8)
Inpatient/ICU admission	25 (6.4)	39 (8.5)	41 (8.5)	36 (6.6)	40 (6.5)	38 (6.2)	40 (4.6)	39 (3.8)	52 (4.3)	39 (3.5)	389(5.3)
Season											
Summer	112 (28.5)	130 (28.3)	116 (24.0)	153 (28.2)	158 (25.7)	146 (23.8)	241 (27.8)	253 (24.5)	302 (25.2)	272 (24.6)	1883 (25.8)
Fall	101 (25.7)	100 (21.8)	125 (25.9)	123 (22.7)	143 (23.3)	168 (27.4)	229 (26.4)	274 (26.6)	349 (29.1)	271 (24.5)	1883 (25.8)
Winter	95 (24.2)	125 (27.2)	111 (23.0)	134 (24.7)	143 (23.3)	135 (22.0)	224 (25.8)	273 (26.5)	249 (20.8)	274 (24.8)	1763 (24.1)
Spring	85 (21.6)	104 (22.7)	131 (27.1)	132 (24.4)	171 (27.8)	164 (26.8)	173 (20.0)	231 (22.4)	300 (25.0)	290 (26.2)	1781 (24.4)

Abbreviations: ED, emergency department; FIA, food-induced anaphylaxis; ICU, intensive care unit.

^a Values are median (interquartile range) or No. of patients (%) of FIA ED visits in children.



Supplemental Table 2. Pediatric FIA ED Visit Rates by Trigger and Age Group, 2005-2014

Trigger	Year ^a										<i>P</i>	
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Value	% Change
Age, 0-2 y												
Peanut	3.54	5.59	5.60	7.34	6.36	6.30	7.64	9.23	8.59	8.41	<0.001	137.6%
Shellfish/fish	*	*	*	*	*	*	*	*	*	*	0.25	20.6%
Tree nuts/seeds	*	2.74	1.83	1.47	2.37	4.07	3.37	2.49	4.17	*	0.004	744.4%
Milk	*	*	*	*	*	*	*	*	*	*	0.002	201.6%
Egg	*	*	*	*	*	*	*	*	*	*	<0.001	163.2%
Fruit/Vegetable/Other	1.50	1.79	2.48	2.94	4.49	3.02	3.37	3.62	5.64	4.53	0.002	302.8%
Unspecified	3.22	3.37	4.09	5.20	4.61	4.59	6.86	6.36	7.73	6.08	<0.001	89.0%
Age, 3-6 y												
Peanut	3.30	4.09	3.80	4.27	5.42	6.12	8.80	8.49	11.30	6.48	0.004	96.1%
Shellfish/fish	*	*	*	*	*	*	*	*	*	*	0.31	15.0%
Tree nuts/seeds	2.03	1.83	1.94	2.41	2.75	3.36	6.01	5.96	7.07	6.39	<0.001	215.3%
Milk	*	*	*	*	*	*	*	*	*	*	0.006	436.9%
Egg	*	*	*	*	*	*	*	*	*	*	0.09	100.0%
Fruit/Vegetable/Other	1.65	1.61	1.42	1.40	2.50	2.50	2.96	4.33	4.07	3.54	<0.001	189.0%
Unspecified	2.18	3.36	3.73	4.27	4.42	5.78	5.42	7.02	7.89	6.39	<0.001	193.6%

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Unspecified	3.30	4.09	3.80	4.27	5.42	6.12	8.80	8.49	11.30	6.48	0.004	96.1%
Age, 7-12 y												
Peanut	1.35	1.41	1.33	1.93	2.37	2.38	3.57	3.79	4.98	4.34	<0.001	220.6%
Shellfish/fish	*	*	*	*	*	*	*	*	*	*	0.01	188.4%
Tree nuts/seeds	0.97	0.56	0.57	0.84	1.89	1.67	3.15	3.18	3.49	3.76	<0.001	289.4%
Milk	*	*	*	*	*	*	*	*	*	*	0.01	68.2%
Egg	*	*	*	*	*	*	*	*	*	*	0.01	100.0%
Fruit/Vegetable/Other	0.68	0.61	*	0.79	1.10	1.51	1.63	2.42	3.09	3.61	<0.001	293.0%
Unspecified	1.55	1.41	1.38	1.43	2.00	2.32	3.99	4.24	4.48	4.65	<0.001	200.8%
Age, 13-17 y												
Peanut	0.94	1.07	1.69	1.82	2.54	1.87	3.69	4.52	4.64	5.96	<0.001	535.1%
Shellfish/fish	*	*	*	*	*	*	*	*	*	*	0.01	49.5%
Tree nuts/seeds	*	0.59	0.82	0.68	2.12	1.37	2.24	3.19	3.46	*	<0.001	100.0%
Milk	*	*	*	*	*	*	*	*	*	*	0.06	97.9%
Egg	*	*	*	*	*	*	*	*	*	*	0.01	100.0%
Fruit/Vegetable/Other	0.83	1.02	1.31	1.54	1.75	2.12	2.12	2.72	4.19	3.82	<0.001	298.8%
Unspecified	0.88	1.66	2.07	2.22	3.39	2.81	4.17	5.33	4.59	5.55	<0.001	527.5%

Abbreviations: ED, emergency department; FIA, food-induced anaphylaxis.

^a Values are No. of FIA ED visits per 100,000 enrollees younger than 18 years.

*Cells had 10 or fewer observations, data have been suppressed to protect patient confidentiality

Supplemental Table 3. Rates of FIA ED Visits by ED Disposition and Age Group, Using Only Method 1 for Patient Identification, 2005-2014

Category	Year										P	%
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Value	Change
Number of anaphylaxis-related ED visits ^a	7.31	8.04	9.01	10.3	12.19	13.84	18.65	21.21	24.92	25.83	<0.001	253.4%
All ED FIA visits ^a	5.24	5.71	6.33	7.49	9.22	9.60	13.53	15.10	17.53	17.52	<0.001	234.2
Age, y ^a												
0-2	9.01	11.80	12.28	16.16	17.20	17.46	21.76	21.94	26.14	25.24	<0.001	180.0
3-6	7.28	8.98	9.31	9.86	12.77	14.23	19.29	20.65	24.63	19.61	<0.001	169.2
7-12	4.01	2.87	3.19	4.25	6.10	6.05	9.55	11.26	12.95	13.96	<0.001	247.9
13-17	3.20	3.43	4.75	5.12	6.35	6.62	10.16	12.39	13.82	16.58	<0.001	417.5
ED FIA visit disposition ^b												
FIA ED discharge	82.0	78.9	72.8	78.0	74.2	76.2	76.0	76.8	78.0	77.9	0.59	-5.0

FIA observation	10.9	12.2	17.8	15.0	18.8	17.6	19.3	19.3	17.3	18.3	0.013	67.9
FIA inpatient/ICU												
admission	7.1	8.9	9.4	7.0	7.0	6.2	4.7	3.9	4.7	3.8	<0.001	-46.5

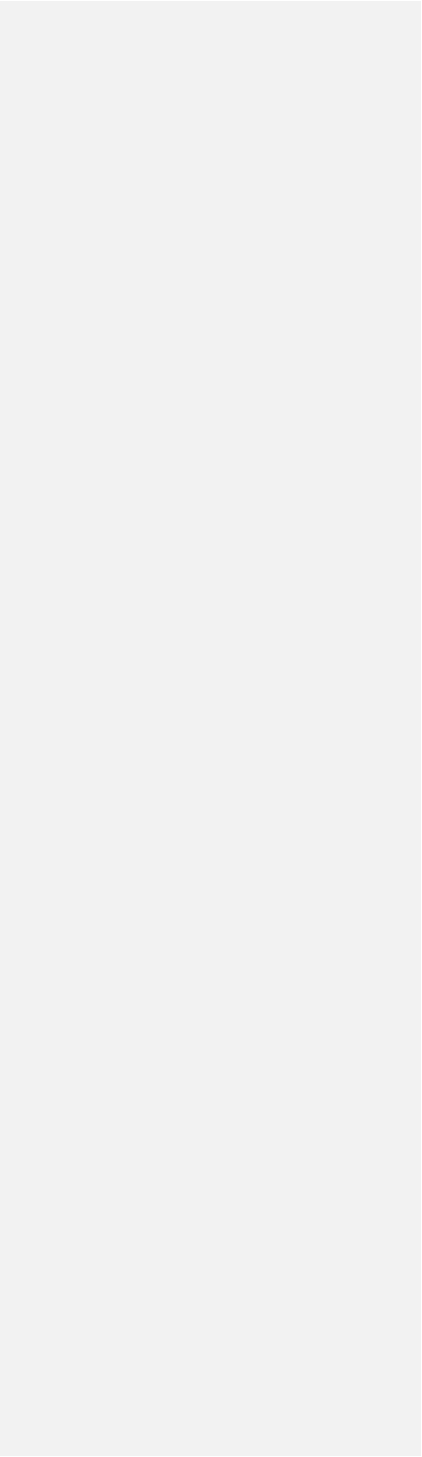
Abbreviations: ED, emergency department; FIA, food-induced anaphylaxis; ICU, intensive care unit.

^a Values are No. of visits per 100,000 enrollees younger than 18 years unless noted otherwise.

^b Values are percentage of FIA-related ED visits among patients younger than 18 years unless noted otherwise.

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