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Trends in U.S. emergency department visits for anaphylaxis among infants and toddlers: 2006-2015

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Title: Trends in U.S. emergency department visits for anaphylaxis among infants and toddlers: 2006-2015

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ABSTRACT

Background: Anaphylaxis is a potentially life-threatening allergic reaction. The overall prevalence of anaphylaxis appears to be rising in children, but temporal trends among infants and toddlers are not well studied.

Objective: To characterize the trends in U.S. emergency department (ED) visits and hospitalizations among infants and toddlers with anaphylaxis from 2006-2015.

Methods: We conducted a study of temporal trends in anaphylaxis among children (age <18 years) and, more specifically, infants and toddlers (age <3 years) presenting to the ED between 2006-2015 using a large, nationally representative database. For internal consistency, we defined anaphylaxis using ICD-9-CM diagnosis codes and excluded visits with ICD-10-CM (late 2015). We calculated trends in the number and proportion of ED visits and hospitalizations and used multivariable logistic regression to identify predictors of hospitalization.

Results: Among infants and toddlers, the proportion of ED visits for anaphylaxis per year increased from 20 per 100,000 visits to 50 per 100,000 visits ($P_{\text{trend}} < 0.001$). The rate of ED visits for anaphylaxis increased from 15 to 32 ED visits per 100,000 population of infants and toddlers ($P_{\text{trend}} < 0.001$). Food was the most commonly identified trigger. The proportion of hospitalization among anaphylaxis-related ED visits decreased from 19% to 6% ($P_{\text{trend}} < 0.001$). Among ED patients, those more likely to be hospitalized were male, privately insured, from higher income families, and presenting to urban, metropolitan teaching hospital EDs.

Conclusion: In a large, nationally representative US database, from 2006 to 2015, ED visits by infants and toddlers with anaphylaxis increased, while hospitalization of these patients decreased.

Highlights box

What is already known about this topic? Little is known about trends in ED visits and

hospitalizations for anaphylaxis among infants and toddlers in the US.

What does the article add to our knowledge? Emergency department visits for anaphylaxis are

rising over time, while the proportion hospitalized are declining.

How does this study impact current management guidelines? These results suggest that

declining hospitalizations among infants and toddlers with anaphylaxis is not due to a decline in

prevalence of anaphylaxis.

Key Words: anaphylaxis, allergic reaction, children, food allergy, infants, emergency

department

Abbreviations:

EAI: Epinephrine auto-injector

ED: Emergency department

FIA: Food-induced anaphylaxis

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

ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification

NEDS: Nationwide Emergency Department Sample

INTRODUCTION

Anaphylaxis is a severe and potentially fatal allergic reaction. In the US, the lifetime prevalence of anaphylaxis is approximately 5% and appears to be rising.¹ In children, the rates of anaphylaxis also appear to be rising, but little is known about the nationwide trends in emergency department (ED) visits among infants and toddlers with anaphylaxis.²⁻⁴ Anaphylaxis among infants and toddlers is unique due to high rates of food-induced anaphylaxis (FIA), a variable clinical presentation, and few children (families) owning an epinephrine autoinjector (EAI) at the time of reaction.⁵⁻⁸ Additionally, infants and toddlers may have limited access to appropriate weight-based dosing of EAI at the time of initial reaction.

In this vulnerable population of infants and toddlers, anaphylaxis is an emerging risk as a growing number of infants and toddlers are exposed to potential food allergens (e.g., peanut) early in life. The aim of this study is to describe the trends in ED visits among children, including infants and toddlers, with overall acute allergic reactions (AAR) and anaphylaxis in the US. We analyzed data from a large, nationally representative, all-payer database from 2006-2015. Our study was conducted prior to implementation and dissemination of the updated food allergy introduction guidelines in 2017.⁹

METHODS

We conducted a cohort study of the trends in US ED visits for acute allergic reactions and anaphylaxis among infants and toddlers (age <3 years) and older children (age 3 to <18 years), from 2006-2015. To maintain internal validity, we excluded data from the fourth quarter of 2015 after the transition to following *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) coding.

Data Sources

We analyzed data from the Healthcare Cost and Utilization Project (HCUP) Nationwide Emergency Department Sample (NEDS), a nationally representative database of ED visits, maintained by the Agency for Healthcare Research and Quality (AHRQ).¹⁰ NEDS is the largest all-payer ED database in the US and provides a nationally-representative sample using weighted estimates of >143 million ED discharges per year. The data are protected by a Data Use Agreement. This study was approved by the local Institutional Review Board.

Study population

We utilized the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes to identify ED visits with diagnosis codes as follows:

Anaphylaxis: anaphylactic shock due to unspecified food (995.60), anaphylactic shock due to specified food (995.61-995.69) and other anaphylactic shock (995.00). The anaphylaxis definition corresponds to Method 1 of the previously validated algorithm by Harduar-Morano.¹¹ This anaphylaxis definition includes FIA, in addition to other non-food triggers of anaphylaxis.

Overall acute allergy reaction (AAR): allergy unspecified (995.3), dermatitis due to ingested food (693.1), anaphylactic shock due to unspecified food (995.60), anaphylactic shock due to specified food (995.61-995.69) and other anaphylactic shock (995.00). This is the broadest category of reaction. Overall AAR contains the codes for anaphylaxis, FAAR and FIA as well as additional codes related to allergic reactions.

Food-induced anaphylaxis (FIA): anaphylactic shock due to unspecified food (995.60) and anaphylactic shock due to specified food (995.61-995.69). FIA includes only the anaphylaxis codes directly related to FIA.

Overall food-induced acute allergic reaction (FAAR): dermatitis due to ingested food (693.1), anaphylactic shock due to unspecified food (995.60), anaphylactic shock due to specified food (995.61-995.69). Overall FAAR includes the codes for FIA and those within AAR that are associated with food-induced allergy.

These 4 categories of allergic reactions (anaphylaxis, AAR, FIA, FAAR) are not mutually exclusive but rather represent 4 grouping of ICD-9-CM codes based on potential reaction severity and trigger. When available, trigger of reaction was determined by specific ICD-9-CM code (e.g. anaphylaxis due to specified food, 995.61-995.69).

Outcomes

The primary outcome was ED visit disposition (e.g. hospitalization) for anaphylaxis among infants and toddlers (age <3 years) in the US. The secondary outcome included epinephrine

administration in the ED determined by current procedural terminology (CPT) code J0170 (2006-2010) and J0171 (2011-2015).

Covariates

We evaluated multiple covariates including patient age, sex, expected payer, median household income quartiles (by ZIP Code), discharge quarter, hospital region, hospital designation (urban vs. rural), and hospital teaching status.

Statistical Analyses

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). Data are presented as proportions with 95% confidence intervals (95% CIs) or medians with interquartile ranges (IQR), as appropriate. We calculated trends in the number and proportion of ED visits per 100,000 visits and hospitalizations during the study period using appropriate survey weighting. Rate of ED visits were calculated per 100,000 of the baseline US population of children for the corresponding year from US census data.

To examine predictors of hospital admission among infants and toddlers presenting to the ED with anaphylaxis, we performed multivariable logistic regression modeling. We included multiple covariates in the model selected *a priori* based on clinical knowledge. All P values were two-tailed, with $P < 0.05$ considered statistically significant.

RESULTS

The number and proportion of ED visits among infants and toddlers for anaphylaxis, overall AAR, FIA and overall FAAR increased significantly over the study period (**Table I, Figure I**). Among infants and toddlers, the proportion of ED visits for anaphylaxis was 20 per 100,000 visits in 2006 and increased to 50 per 100,000 visits in 2015 ($P_{\text{trend}} < 0.001$). Similarly, the ED visits rate for anaphylaxis among infants and toddlers increased from 15 per 100,000 US population to 32 per 100,000 US population ($P_{\text{trend}} < 0.001$). ED visits for anaphylaxis rose for all age groups of children over time in the US (**Figure II**). The number and proportion of ED visits for overall AAR, FIA and overall FAAR among all age groups of children (age < 18 years) also increased (**Online Repository Table EI**).

Characteristics of ED Visits for Anaphylaxis Among Infants and Toddlers

ED visits among infants and toddlers were highest among males, privately insured, in the highest median household income quartile, in the Northeast with presentation to urban and metropolitan teaching hospitals (**Table II, Online Repository Table EII**).

FIA was the most commonly identified type of anaphylaxis among infants and toddlers throughout the study period, accounting for 75% of reactions in 2006 and 68% reactions in 2015. Of those infants and toddlers with FIA and an identified trigger, peanut was the most common (**Figure III**).

ED Visit Disposition Among Infants and Toddlers with Anaphylaxis

The proportion of infants and toddlers who presented to the ED for anaphylaxis and were then admitted to the hospital decreased significantly during the study period from 19% in 2006 to 6% in 2015 ($P_{\text{trend}} < 0.001$) (**Figure IV**).

Predictors of Hospitalization

Demographic and hospital characteristics predicting hospitalization include male sex, private insurance, highest quartile of median household income, and presentation to an urban or metropolitan teaching hospital (**Table III**).

Epinephrine Administration in the ED

The rate of epinephrine administration in the ED among infants and toddlers presenting with anaphylaxis increased greatly during the study period from 5% in 2006 to 24% in 2015 ($P_{\text{trend}} < 0.001$) (**Table II**).

DISCUSSION

Using nationally representative data, we report that the number, proportion and rate of US ED visits among infants and toddlers presenting with anaphylaxis, which more than doubled between 2006 and 2015. ED visits also rose for all age groups of children presenting with anaphylaxis, overall AAR, FIA and overall FAAR.

The rising ED visits seen in our study suggest the underlying prevalence of anaphylaxis is increasing in all children and particularly among the vulnerable population of infants and toddlers. These results are consistent with other published studies showing rising ED visits for anaphylaxis among children.^{8,12-15} Our study focuses on infants and toddlers as this population is understudied. Anaphylaxis among infants and toddlers is unique due to high rates of FIA without a preceding diagnosis of food allergy and thus potentially limited access to EAI at the time of reaction.^{5, 16}

We report that food-induced reactions, including FIA and overall FAAR, account for most reactions among infants and toddlers. Importantly, this study was conducted prior to the publication of the LEAP trial in 2015 and publication and dissemination of the 2017 NIH Addendum Guidelines to Prevent Peanut Allergy.^{9, 17} The implementation of these guidelines may lead to increased exposure to common food allergens in early life, especially among high-risk children. Our study reports rising rates of anaphylaxis and acute allergic reactions among infants and toddlers even prior to this paradigm shift. The increasing prevalence of food allergy is likely a key driving force in the rising ED visits for anaphylaxis.^{18, 19} Other factors to consider include increased diagnosis due to rising awareness of anaphylaxis and food allergy among

children. When sufficient data are available for the era of early allergen introduction (estimated late 2021) future studies will be needed to study the effect of this paradigm shift.

We report the highest rates of anaphylaxis among infants and toddlers occurred in males, with private insurance, in the Northeast. The predominance of male sex has been consistently reported in studies of anaphylaxis among children, though the underlying reason is not clear.^{5, 20-21} Our findings are consistent with prior studies showing the highest rate of ED visits and hospitalizations for FIA occurred in the Northeast US.²² The relationship between vitamin D status and food allergy may play a key role in this geographic distribution.^{22,23} Considerable hospital-to-hospital variation has been described for the rates of hospitalization among children with anaphylaxis.²⁴ This regional difference also may represent differences in healthcare utilization patterns or geographic changes in disease prevalence.^{25,26}

Interestingly, we report a declining trend in hospitalization among infants and toddlers presenting to the ED for anaphylaxis. There are variable reports of the trends in hospitalizations for anaphylaxis among children in the literature, with little published to date on infants and toddlers. Our group previously reported an overall increase in the rate of hospitalizations from 2000-2009 in children (age <18 years) with FIA in the US using the HCUP Kids' inpatient database. However, among children aged 0-2 years, there was no significant increase in the rate of hospitalization.²⁰ A more recent study, using data from the HCUP Nationwide Inpatient Sample, found a generally stable number of hospitalizations of children (age <18 years) with anaphylaxis from 2001-2014; however, there was no specific analysis of infants and toddlers children aged <3 years.³ In another study of children presenting with FIA, using data from

privately insured or Medicare Advantage enrollees, the rates of hospitalization from 2005-2014 were stable, though specific trends in infants and toddlers were not reported.⁸ A study in Australia found rising rates of hospitalization among children with anaphylaxis in 2011-2012 compared to 1999-1999, with the highest number of hospitalizations occurring among children 0-4 years of age.²⁶ Our group recently reported that anaphylaxis hospitalizations among infants and toddlers (age < 3 years) in the US were stable from 2006-2015. This study was conducted using the National Inpatient Sample (NIS), maintained by HCUP.²⁷ This pattern suggests that the rates of hospitalization may differ by age, with infants and toddlers representing a unique patient population.

The reasons for the declining rates of hospitalization in our study are not known. Possible reasons for the decline include improved management of anaphylaxis, low severity of presentation and changes in patterns of healthcare utilization. Early and appropriate use of epinephrine in FIA has been shown to decrease risk of hospitalization.²⁸ In our study, we report a more than 4-fold rise in ED administration of epinephrine over time, which may lead to decreased need for hospitalization. While we are unable to capture pre-hospital administration of epinephrine, this rise in appropriate therapy is reassuring; though there is likely room for continued improvement. As previously published, caregivers of infants and toddlers rarely carry EIA at the time of initial reaction, thus ED administration may be required in a large proportion of patients.⁵ The increase in ED visits for anaphylaxis and AARs may also lead to increasing comfort with diagnosis and management of these conditions and thus decreased need for hospitalization.^{29,30} Through implementation of an evidence-based guideline, one children's hospital was able to successfully decrease hospital admission for children with anaphylaxis

without a rise in the 72 hour ED revisit rate, suggesting that a reduction in hospitalization rates may be due to adherence with guideline-based therapy.³¹

Little is known about the severity of anaphylaxis among infants and toddlers. It is possible that reactions are less severe and thus hospitalization is often not warranted. A study of children presenting to the ED for FIA found that infants and toddlers were more likely to present with skin manifestations and less likely than older children to present with respiratory complaints, suggesting that infants and toddlers to have a less severe presentation of FAI.³² With early introduction in the LEAP trial, serious allergic reactions among participants were not common.¹⁷ A recent study found that children < 2 years of age tended to meet criteria for anaphylaxis less often than older children, though the difference was not significant.³³ This is further supported by the fact that few children hospitalized for FIA require interventions during hospitalization.³⁴

We identified several predictors of hospitalization including male sex, private insurance, and presentation to an urban or metropolitan teaching hospital. These patterns of healthcare utilization may relate to underlying variability in disease prevalence and resources, including availability of ED observation units or differences in access to care. A prior study found significant variability in hospitalization rates among pediatric hospitals in the US.¹¹ There are significant differences in food allergy prevalence between urban and rural populations.²⁵ Patterns of healthcare utilization, resources and health seeking behavior may all differ due to geographic location.²⁴ These factors coupled with the baseline prevalence of food allergy, may affect rates of hospitalization for anaphylaxis.

This study is limited by use of administrative data, which is prone to coding error and diagnostic misclassification. Based on prior studies, anaphylaxis is under diagnosed by ICD-9-CM code and thus we expect that we may be providing an underestimate of the prevalence of anaphylaxis.³⁴ The ability to adjudicate trigger of reaction (e.g. food) is limited to diagnosis code alone; however, our findings of high-rates of FIA are consistent with published studies of anaphylaxis in children.^{3, 8, 12} In addition, we found similar results using a broad category (overall AAR) and a more specific codes focused on anaphylaxis. Our ability to capture epinephrine administration is limited to procedure codes and thus does not capture appropriate administration in the pre-hospital setting. Due to the transition from ICD-9-CM and ICD-10-CM in late 2015, we have data only from the first 3 quarters of 2015; however, the overall trends among infants and toddlers are present prior to 2015 and weighted estimates were used.

The strengths of this study include the use of a large, nationally representative, all-payer database with a 10-year study period that provides the ability to study US trends over time. Our study focuses on a specific subset of very young children (infants and toddlers), who are vulnerable and rarely studied in anaphylaxis. Based on the nature of our data, the results of this study are widely generalizable.

In summary, the rates of ED visits for anaphylaxis among children in the US, including infants and toddlers, are rising over time. Infants and toddlers are a vulnerable and understudied population with high rates of FIA. Hospitalizations among infants and toddlers are declining. While the reasons for this are not known, we hypothesize that these trends may be attributable to improved management of anaphylaxis, low severity of reactions and changes in health care

313 utilization. In the era of early allergen introduction, anaphylaxis is an emerging risk for infants
314 and toddlers, and it is imperative that we continue to study trends in prevalence, severity and
315 healthcare utilization in this unique population.

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FIGURE LEGENDS

Figure I. U.S. emergency department visits among infants and toddlers for anaphylaxis and overall acute allergic reactions, 2006-2015

Abbreviations: AAR, acute allergic reaction; FAAR, food-induced acute allergic reaction; FIA, food-induced anaphylaxis

Overall AAR includes codes for anaphylaxis, FIA and FAAR. Anaphylaxis include FIA and non-food related anaphylaxis. Overall FAAR includes FIA and other food-related codes.

Figure II. U.S. emergency department visits for anaphylaxis among all children (age <18 years), 2006-2015

Figure III. Identified food trigger among infants and toddlers presenting to US emergency departments with food-induced anaphylaxis 2006-2015

Figure IV. Proportion of US emergency department visits and hospitalizations among infants and toddlers with anaphylaxis, 2006-2015

Abbreviations: ED- emergency department

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Table EI. US emergency department visits for anaphylaxis and allergic reactions among children (age <18 years), 2006-2015

ED Visit Diagnosis*	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P _{trend}
Weighted Visits per 100,000 Visits											
Anaphylaxis											
0 to <3	20 (20, 20)	20 (20, 20)	20 (20,30)	20 (20, 30)	30 (20, 30)	30 (30, 40)	40 (30, 40)	40 (30, 50)	50 (50, 60)	50 (50, 60)	< 0.001
3 to <6	28 (22, 34)	24 (20, 28)	34 (28, 40)	35 (29, 42)	40 (31, 48)	49 (39, 58)	55 (47, 63)	62 (52, 73)	78 (65, 91)	80 (67, 93)	< 0.001
6 to <12	28 (22, 34)	26 (22, 30)	30 (25, 35)	30 (25, 35)	40 (32, 47)	48 (40, 56)	61 (53, 69)	71 (61, 81)	88 (75, 100)	87 (73, 100)	< 0.001
12 to <18	33 (26, 40)	34 (29, 39)	39 (34, 45)	38 (33, 43)	46 (39, 53)	54 (47, 61)	67 (59, 75)	74 (65, 83)	98 (86, 111)	115 (103, 128)	< 0.001
Overall AAR											
0 to <3	404 (379,428)	415 (387,444)	472 (442,502)	517 (486,548)	559 (523,594)	601 (563,639)	627 (584,671)	645 (588,703)	659 (618, 701)	737 (690, 785)	< 0.001
3 to <6	575 (542,608)	566 (529,602)	631 (592,671)	675 (636,714)	778 (731,825)	828 (775,882)	855 (800,910)	878 (810,946)	941 (885,998)	942 (886,998)	< 0.001
6 to <12	553 (524,582)	562 (527,597)	637 (601,674)	642 (607,678)	763 (718,808)	805 (752,858)	889 (838,940)	910 (842,977)	974 (921,1027)	963 (915,1010)	< 0.001
12 to <18	457 (435,479)	466 (441,492)	500 (476,525)	542 (515,569)	617 (586,648)	673 (639,707)	726 (693,759)	765 (722,808)	823 (783, 862)	843 (810, 876)	< 0.001
FIA											

0 to <3	16 (12, 19)	15 (12, 18)	20 (16, 23)	18 (14, 22)	20 (16, 24)	25 (20, 30)	28 (24, 33)	30 (25, 35)	37 (32, 43)	38 (30, 46)	< 0.001
3 to <6	21 (16, 26)	17 (14, 20)	25 (20, 30)	26 (21, 32)	30 (24, 36)	34 (27, 41)	39 (32, 45)	41 (33, 48)	50 (41, 59)	47 (39, 55)	< 0.001
6 to <12	17 (13, 21)	15 (12, 18)	19 (15, 22)	20 (16, 23)	26 (21, 32)	30 (24, 36)	40 (34, 45)	44 (36, 52)	51 (44, 59)	49 (40, 58)	< 0.001
12 to <18	17 (13, 22)	19 (16, 23)	22 (18, 25)	21 (18, 25)	26 (21, 30)	29 (25, 34)	39 (34, 45)	41 (34, 47)	55 (47, 63)	61 (54, 69)	< 0.001
Overall FAAR											
0 to <3	102 (93, 112)	104 (96, 112)	116 (107,126)	111 (103,119)	121 (111,131)	128 (117,138)	131 (121,142)	137 (125,148)	145 (133, 158)	148 (132, 164)	< 0.001
3 to <6	86 (76, 95)	85 (77, 93)	105 (94, 115)	98 (89, 108)	115 (105,125)	118 (107,129)	125 (113,138)	121 (109,132)	135 (121,148)	131 (116, 146)	< 0.001
6 to <12	72 (65, 80)	71 (64, 78)	83 (75, 91)	77 (70, 84)	96 (87, 105)	101 (91, 112)	117 (106,128)	124 (113,135)	135 (123, 147)	127 (113, 142)	< 0.001
12 to <18	68 (61, 75)	68 (63, 74)	75 (68, 82)	75 (68, 81)	86 (79, 93)	91 (84, 99)	106 (96, 116)	109 (99, 120)	131 (118, 143)	137 (124, 149)	< 0.001

Abbreviations: AAR, acute allergic reaction; FIA, food-induced anaphylaxis; FAAR, food-induced acute allergic reaction.

*Overall AAR includes codes for anaphylaxis, FIA and FAAR. Anaphylaxis include FIA and non-food related anaphylaxis. Overall FAAR includes FIA and other food-related codes.

Table EII. Patient and hospital characteristics of US emergency department visits by infants and toddlers (age <3 years) for anaphylaxis, 2006-2015

Characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P _{trend}
Weighted Visits per 100,000 Visits											
Overall	20 (20, 20)	20 (20, 20)	20 (20, 30)	20 (20, 30)	30 (20, 30)	30 (30, 40)	40 (30, 40)	40 (30, 50)	50 (50, 60)	50 (50, 60)	< 0.001
Sex											
Male	20 (20,30)	20 (20, 30)	30 (20,30)	30 (20,30)	30 (20,40)	40 (30,50)	40 (40,50)	50 (40,50)	60 (50,70)	70 (60,80)	< 0.001
Female	20 (10,20)	10 (10,20)	20 (10,20)	20 (10,20)	20 (20,30)	20 (20,30)	30 (20,30)	30 (30,40)	40 (30,50)	40 (30,50)	< 0.001
Primary Health Insurance											
Public	9 (6, 10)	10 (8, 10)	10 (9, 10)	10 (9, 20)	10 (10,20)	20 (10,20)	20 (20,20)	20 (20,30)	30 (30,40)	30 (30,40)	< 0.001
Private	40 (40,50)	40 (30,50)	50 (40,60)	40 (30,50)	60 (40,70)	80 (60,100)	90 (70,100)	100 (80, 110)	130 (110,160)	130 (100,160)	< 0.001
Self-pay	10 (6,20)	9 (3,10)	20 (6,30)	20 (10,30)	7 (2,10)	7 (3,10)	20 (10, 20)	20 (20,30)	30 (20,50)	30 (20,40)	< 0.001
Other	20 (5, 30)	20 (8, 30)	20 (8, 30)	10 (5, 20)	20 (10,40)	30 (20, 50)	50 (30, 70)	50 (20,70)	50 (30,70)	60 (30,80)	< 0.001
Median household income quartile*											
1 (lowest)	10 (8, 10)	10 (8, 10)	10 (10,20)	10 (8, 20)	10 (8, 20)	20 (10, 20)	20 (20, 30)	20 (20,30)	30 (30,40)	30 (20,40)	< 0.001
2	10 (9, 20)	10 (8, 10)	10 (10,10)	20 (10,20)	20 (10,30)	20 (20, 30)	20 (20, 30)	30 (20,30)	40 (30,40)	40 (30,50)	< 0.001
3	20 (20,30)	30 (20,30)	30 (20,30)	30 (20,30)	30 (20,40)	40 (30, 50)	40 (40, 50)	40 (40,50)	60 (50,80)	60 (50,80)	< 0.001
4 (highest)	50 (40,60)	50 (40,60)	70 (50,90)	60 (50,80)	70 (60,90)	70 (60, 90)	90 (70,100)	100 (80, 130)	140 (110,160)	140 (110,180)	< 0.001
Discharge Quarter											
First quarter (Jan - Mar)	10 (10,20)	10 (10,20)	20 (10,20)	20 (10,20)	20 (10,30)	20 (20, 30)	30 (30, 40)	30 (20,40)	40 (30,50)	40 (30,50)	< 0.001
Second quarter (Apr - Jun)	20 (10,30)	20 (20,30)	20 (20,30)	30 (20,30)	30 (20,40)	30 (30, 40)	40 (30, 50)	40 (30,50)	60 (50,70)	60 (50,70)	< 0.001
Third quarter (Jul - Sep)	30 (20,40)	20 (20,30)	30 (20,40)	30 (20,30)	30 (20,30)	40 (30, 50)	40 (40, 50)	50 (40,60)	60 (50,70)	70 (50,80)	< 0.001
Fourth quarter (Oct - Dec)	20 (20,30)	20 (10,20)	30 (20,30)	20 (20,30)	30 (20,30)	40 (30, 40)	30 (20, 40)	40 (30,50)	50 (40,60)	-	-
Hospital Region											
Northeast	30 (20,50)	30 (20,40)	40 (30,50)	30 (20,40)	40 (30,60)	40 (30, 50)	60 (40, 70)	50 (40, 60)	100 (70, 120)	110 (70, 140)	< 0.001

Midwest	20 (10,30)	20 (10,20)	20 (20,30)	20 (10,30)	30 (20,40)	40 (20, 50)	40 (30, 50)	40 (30,50)	50 (40,60)	50 (30,70)	< 0.001
South	20 (10,20)	10 (10,20)	20 (10,30)	20 (10,30)	20 (10,30)	30 (20, 40)	30 (20, 40)	40 (30,40)	40 (30,50)	50 (30,60)	< 0.001
West	20 (10,20)	20 (10,30)	20 (10,30)	20 (10,40)	20 (10,20)	30 (20, 30)	40 (20, 50)	40 (20,60)	40 (30,50)	40 (30,50)	< 0.001
Hospital Designation											
Urban	20 (20,30)	20 (20,20)	30 (20,30)	20 (20,30)	30 (20,30)	30 (30, 40)	40 (30, 40)	40 (30,50)	60 (50,60)	60 (50,70)	< 0.001
Rural	20 (10,30)	10 (4, 20)	9 (3, 10)	9 (2, 20)	20 (8, 20)	10 (2, 20)	20 (8, 20)	10 (5, 20)	20 (10,30)	20 (6, 30)	0.74
Hospital Status											
Metropolitan, Non-teaching	20 (10,20)	20 (10,20)	20 (10,30)	20 (10,30)	20 (10,30)	20 (20, 30)	30 (20, 40)	40 (30,40)	30 (20,40)	40 (30,40)	< 0.001
Metropolitan Teaching	30 (20,30)	30 (20,30)	30 (30,40)	30 (20,40)	40 (30,50)	50 (40, 60)	50 (40, 60)	50 (40,60)	70 (60,80)	70 (50,80)	< 0.001
Non-Metropolitan	10 (7, 20)	10 (6, 10)	10 (5, 10)	9 (5, 10)	10 (7, 20)	10 (6, 10)	20 (10, 20)	20 (10, 20)	20 (10,20)	20 (20,30)	< 0.001
Epinephrine administered in ED (Weighted percent)	5 (2,8)	4 (1,5)	8 (4,12)	10 (5,14)	11 (7,16)	11 (5,16)	14 (10,19)	12 (8,16)	19 (13,24)	24 (17,30)	< 0.001

*Median Household Income Quartile 1) 0-25th percentile 2) 26th-50th percentile 3) 51st-75th percentile 4) 76th-100th percentile

TABLES

Table I. US emergency department visits for allergic reactions among infants and toddlers (age <3 years), 2006-2015

ED Visit Diagnosis*	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P _{trend}
Weighted Visits per 100,000 Visits											
Anaphylaxis	20 (20, 20)	20 (20,20)	20 (20,30)	20 (20, 30)	30 (20, 30)	30 (30, 40)	40 (30, 40)	40 (30, 50)	50 (50, 60)	50 (50, 60)	< 0.001
Overall AAR	404 (379, 428)	415 (387, 444)	472 (442, 502)	517 (486, 548)	559 (523, 594)	601 (563, 639)	627 (584, 671)	645 (588, 703)	659 (618, 701)	737 (690, 785)	< 0.001
FIA	16 (12, 19)	15 (12, 18)	20 (16, 23)	18 (14, 22)	20 (16, 24)	25 (20, 30)	28 (24, 33)	30 (25, 35)	37 (32, 43)	38 (30, 46)	< 0.001
Overall FAAR	102 (93, 112)	104 (96, 112)	116 (107, 126)	111 (103, 119)	121 (111, 131)	128 (117, 138)	131 (121, 142)	137 (125, 148)	145 (133, 158)	148 (132, 164)	< 0.001

Abbreviations: AAR, acute allergic reaction; FIA, food-induced anaphylaxis; FAAR, food-induced acute allergic reaction.

*Overall AAR includes codes for anaphylaxis, FIA and FAAR. Anaphylaxis include FIA and non-food related anaphylaxis. Overall FAAR includes FIA and other food-related codes.

Table II. Patient and hospital characteristics of US emergency department visits by infants and toddlers (age <3 years) for anaphylaxis, 2006-2015

Characteristics	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P _{trend}
	Weighted Visits per 100,000 Visits										
Overall	20	20	20	20	30	30	40	40	50	50	< 0.001
Sex											
Male	20	20	30	30	30	40	40	50	60	70	< 0.001
Female	20	10	20	20	20	20	30	30	40	40	< 0.001
Primary Health Insurance											
Public	9	10	10	10	10	20	20	20	30	30	< 0.001
Private	40	40	50	40	60	80	90	100	130	130	< 0.001
Self-pay	10	9	20	20	7	7	20	20	30	30	< 0.001
Other	20	20	20	10	20	30	50	50	50	60	< 0.001
Median household income quartile*											
1 (lowest)	10	10	10	10	10	20	20	20	30	30	< 0.001
2	10	10	10	20	20	20	20	30	40	40	< 0.001
3	20	30	30	30	30	40	40	40	60	60	< 0.001
4 (highest)	50	50	70	60	70	70	90	100	140	140	< 0.001
Discharge Quarter											
First quarter (Jan - Mar)	10	10	20	20	20	20	30	30	40	40	< 0.001
Second quarter (Apr - Jun)	20	20	20	30	30	30	40	40	60	60	< 0.001
Third quarter (Jul - Sep)	30	20	30	30	30	40	40	50	60	70	< 0.001
Fourth quarter (Oct - Dec)	20	20	30	20	30	40	30	40	50	-	-
Hospital Region											
Northeast	30	30	40	30	40	40	60	50	100	110	< 0.001
Midwest	20	20	20	20	30	40	40	40	50	50	< 0.001
South	20	10	20	20	20	30	30	40	40	50	< 0.001
West	20	20	20	20	20	30	40	40	40	40	< 0.001
Hospital Designation											
Urban	20	20	30	20	30	30	40	40	60	60	< 0.001
Rural	20	10	9	9	20	10	20	10	20	20	0.74

Hospital Status											
Metropolitan, Non-teaching	20	20	20	20	20	20	30	40	30	40	< 0.001
Metropolitan Teaching	30	30	30	30	40	50	50	50	70	70	< 0.001
Non-Metropolitan	10	10	10	9	10	10	20	20	20	20	< 0.001
Epinephrine administered in ED (Weighted Percent of Visits)	5	4	8	10	11	11	14	12	19	24	< 0.001

*Median Household Income Quartile 1) 0-25th percentile 2) 26th-50th percentile 3) 51st-75th percentile 4) 76th-100th percentile
For 95% confidence intervals please see Online Repository Table EI.

Table III. Predictors of hospitalization after presentation to US emergency department for anaphylaxis among infants and toddlers, 2006-2015

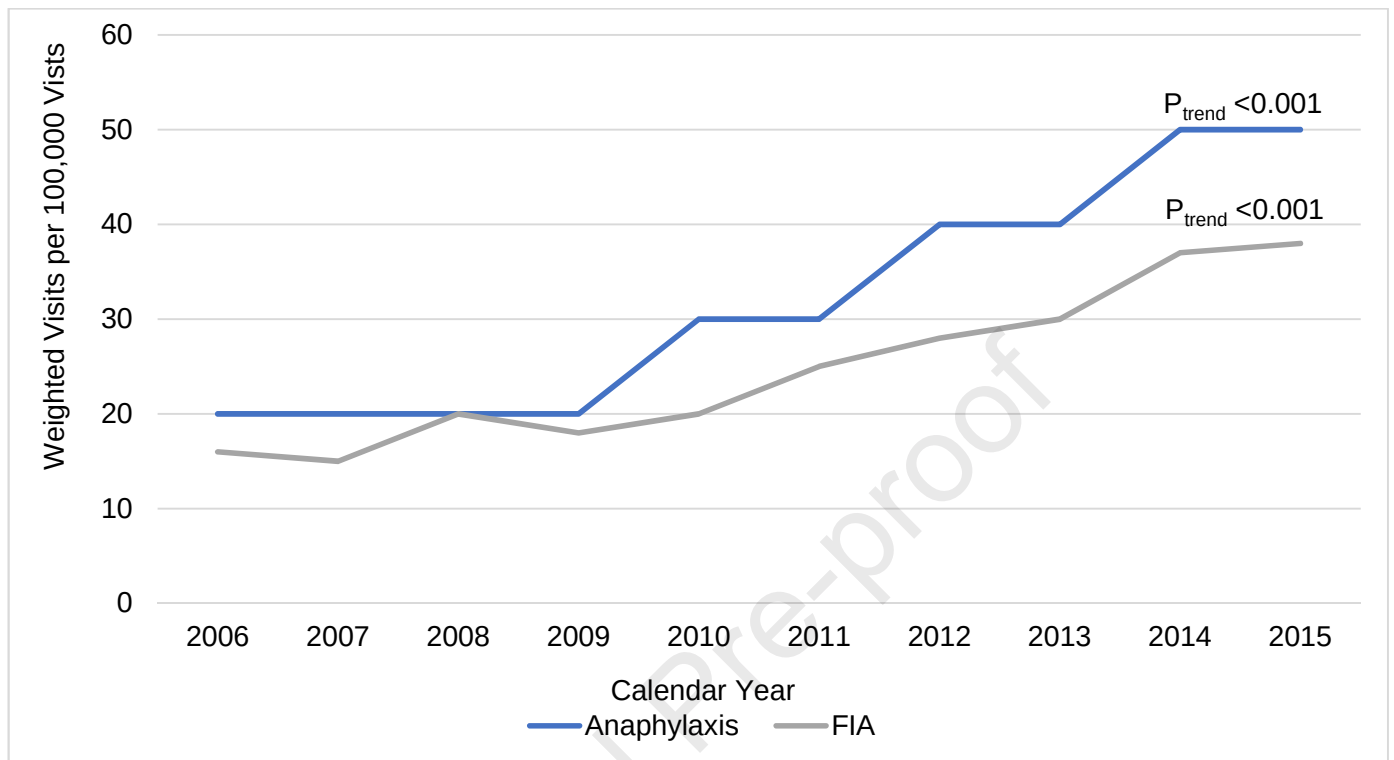
Predictor	Adjusted Odds Ratio (95% Confidence Interval)	P_{trend}
Sex		
Male	1.00 (reference)	-
Female	0.92 (0.92,0.93)	<0.001
Payer		
Public	1.00 (reference)	-
Private	1.12 (1.06,1.19)	<0.001
Self-pay	0.40 (0.37,0.44)	<0.001
Other	1.02 (0.90, 1.14)	0.80
Median Household Income Quartile*		
First (lowest)	1.00 (reference)	-
Second	1.06 (1.00, 1.13)	0.05
Third	1.12 (1.05, 1.20)	0.001
Fourth (highest)	1.28 (1.18, 1.40)	<0.001
Discharge Quarter		
First quarter (Jan - Mar)	1.00 (reference)	-
Second quarter (Apr - Jun)	0.79 (0.78, 0.81)	<0.001
Third quarter (Jul - Sep)	0.77 (0.75, 0.78)	<0.001
Fourth quarter (Oct - Dec)	0.84 (0.83, 0.86)	<0.001
Hospital Region		
Northeast	1.00 (reference)	-
Midwest	0.84 (0.70, 1.02)	0.08
South	1.03 (0.88, 1.21)	0.72
West	1.11 (0.92, 1.33)	0.28
Hospital Designation		
Urban	1.00 (reference)	-

Rural	0.71 (0.62, 0.81)	<0.001
Hospital Status		
Metropolitan, Non-teaching	1.00 (reference)	-
Metropolitan, Teaching	2.65 (2.28, 3.08)	<0.001
Non-metropolitan	0.97 (0.82, 1.14)	0.67

*Median Household Income Quartile 1) 0-25th percentile 2) 26th-50th percentile 3) 51st-75th percentile 4) 76th-100th percentile

Figure I. U.S. emergency department visits among infants and toddlers for anaphylaxis and overall acute allergic reactions, 2006-2015

A. Anaphylaxis and Food-Induced Anaphylaxis



B. Overall Acute Allergic Reactions and Overall Food-induced Acute Allergic Reactions

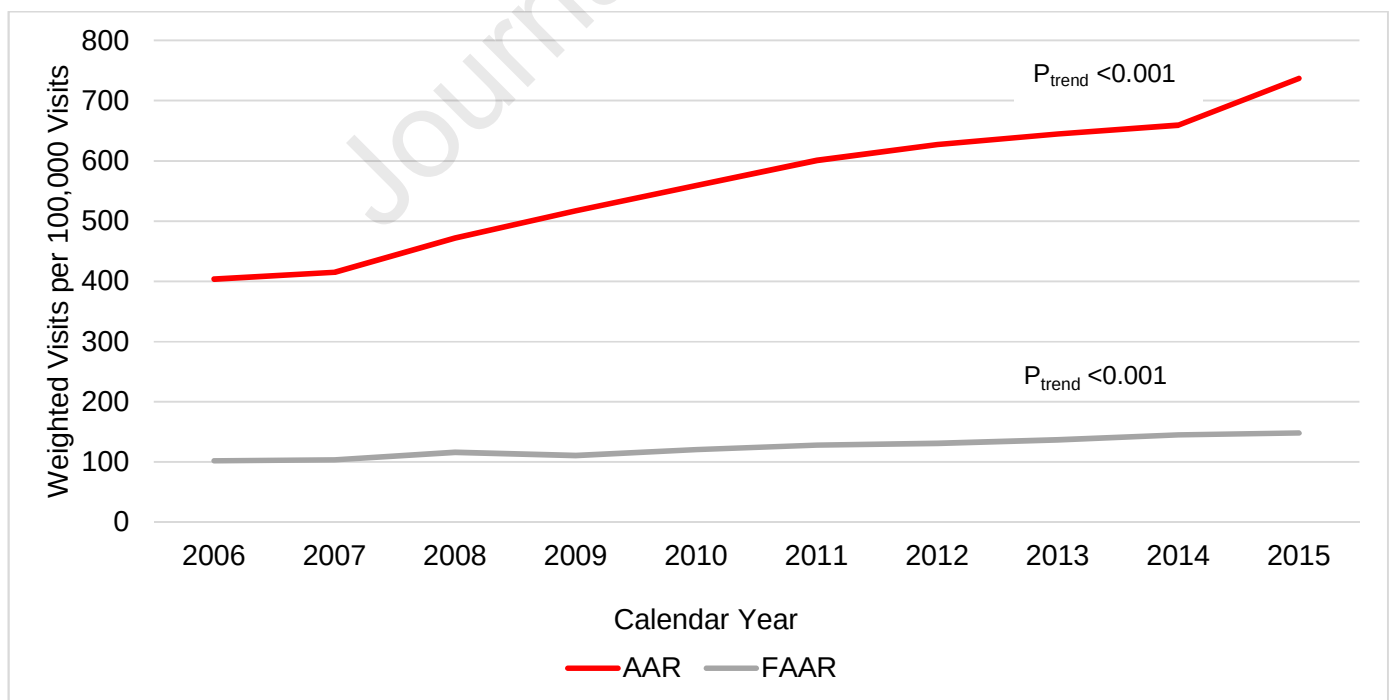


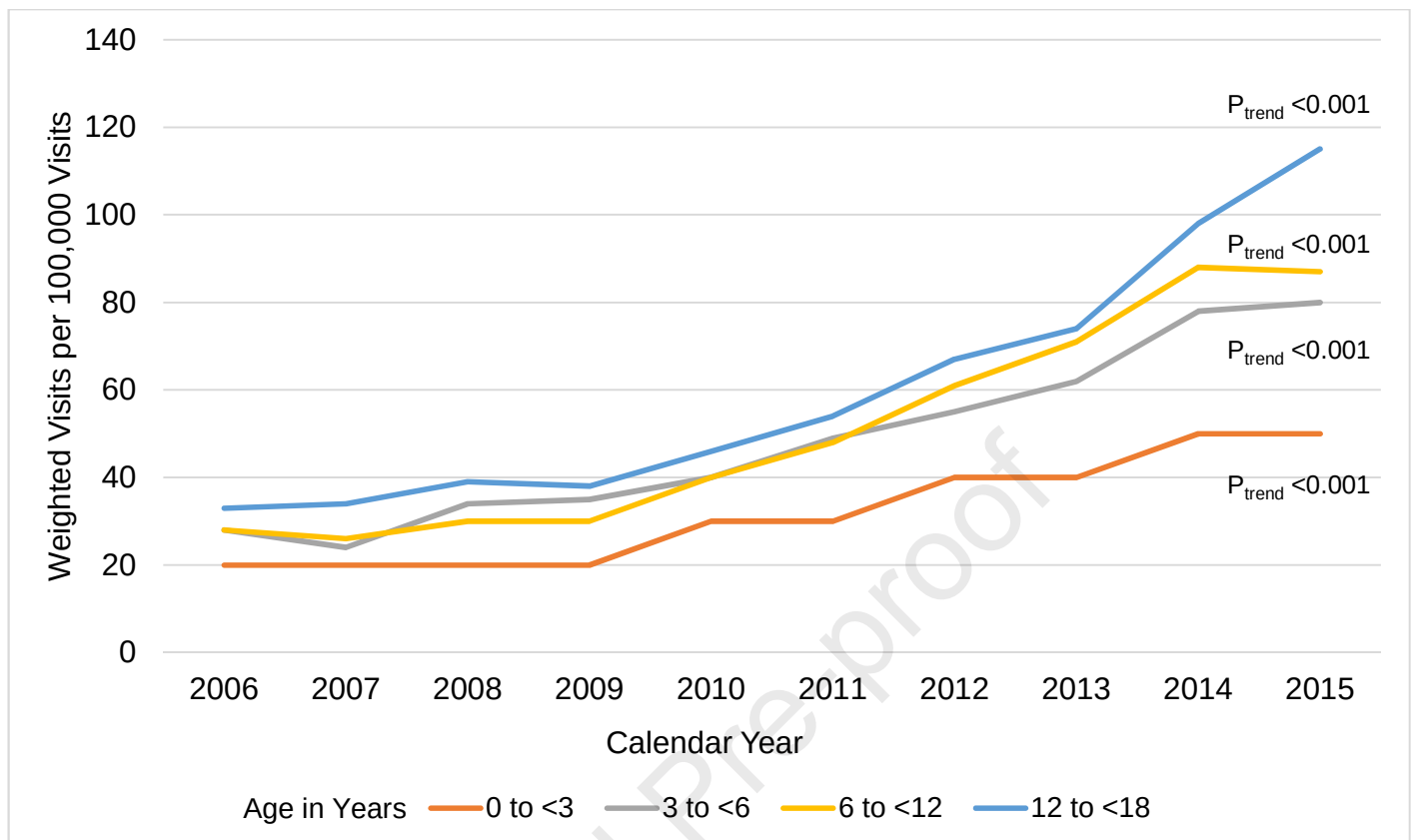
Figure II. U.S. emergency department visits for anaphylaxis among all children (age <18 years), 2006-2015

Figure III. Identified food trigger among infants and toddlers presenting to US emergency departments with food-induced anaphylaxis 2006-2015

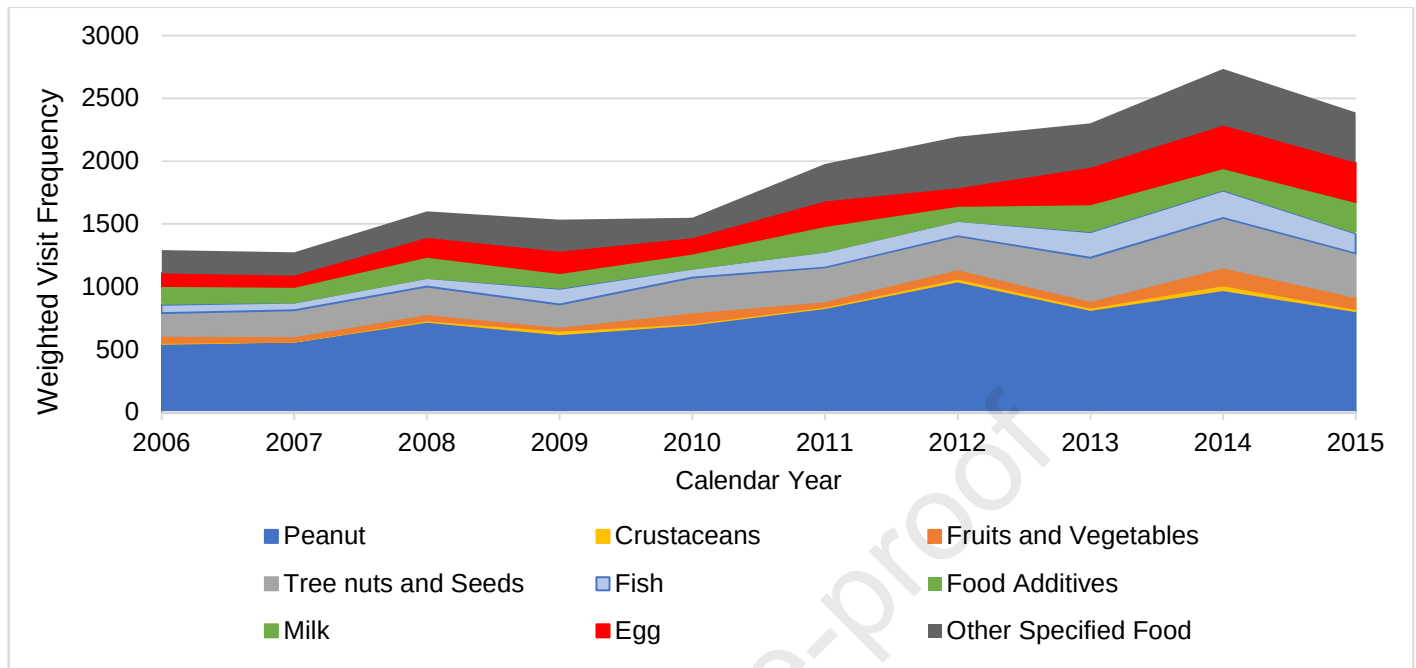


Figure IV. Proportion of US emergency department visits and hospitalizations among infants and toddlers with anaphylaxis, 2006-2015

