



Risk factors for severe anaphylaxis in the United States

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ABSTRACT

Background: Anaphylaxis is an acute systemic allergic reaction and may be life-threatening.

Objective: To assess risk factors associated with severe and near-fatal anaphylaxis in a large observational cohort study.

Methods: We analyzed administrative claims data from Medicare Advantage and privately insured enrollees in the United States from 2005 to 2014. Severe anaphylaxis was defined as anaphylaxis resulting in hospital or intensive care unit (ICU) admission, requiring endotracheal intubation, or meeting criteria for near-fatal anaphylaxis.

Results: Of 38,695 patients seen in the emergency department for anaphylaxis during the study period, 4,431 (11.5%) required hospitalization, 2,057 (5.3%) were admitted to the ICU, 567 (1.5%) required endotracheal intubation, and 174 (0.45%) were classified as having a near-fatal episode. Multivariable analysis revealed that medication-related anaphylaxis (odds ratio [OR], 1.50; 95% confidence interval [CI], 1.38–1.63; $P < .001$), age of 65 years or older (OR, 3.15; 95% CI, 2.88–3.44; $P < .001$), and the presence of cardiac disease (OR, 1.56; 95% CI, 1.50–1.63; $P < .001$) or lung disease (OR, 1.23; 95% CI, 1.16–1.30; $P < .001$) were associated with increased odds of severe anaphylaxis requiring any hospital admission, ICU admission, or intubation or being a near-fatal reaction.

Conclusion: In this large contemporary cohort study, 11.6% of patients had severe anaphylaxis. Age of 65 years or older, medication as a trigger, and presence of comorbid conditions (specifically cardiac and lung disease) were associated with significantly higher odds of severe anaphylaxis. Additional studies examining risk factors for severe anaphylaxis are needed to define risk assessment strategies and establish a framework for management.

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Introduction

Anaphylaxis is an acute systemic allergic reaction and may involve life-threatening airway, breathing, or circulation problems.¹ The lifetime prevalence of anaphylaxis in the United States has been estimated at between 0.5% and 2%,² with a recent study

suggesting a prevalence as high as 5.1%.³ Trends in anaphylaxis-related hospitalizations appear to be increasing, not only in the United States^{4,5} but also in Spain,⁶ the United Kingdom,⁷ and Australia.^{8,9} In the United States, Ma et al⁴ reported that the rate of anaphylaxis-related hospitalizations increased from 21.0 to 25.1 per million population between 1999 and 2009. The severity and outcomes of any anaphylactic episode are unpredictable¹⁰; thus, risk assessment strategies are needed.

An important area of anaphylaxis research has been identifying clinical markers to distinguish those likely to have more severe outcomes and even death from most patients who will have mild to moderate reactions and can safely be discharged home. The study of nonfatal but severe outcomes of anaphylaxis is important because these reactions represent key points of intervention with the potential for improving future outcomes.

Our study objective was to evaluate risk factors associated with increased anaphylaxis severity by studying cases of severe

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anaphylaxis, defined as that resulting in hospital or intensive care unit (ICU) admission, requiring endotracheal intubation, or meeting criteria for a near-fatal reaction.

Methods

Data Source

We conducted an observational study by using data from the OptumLabs Data Warehouse. This database includes administrative data for privately insured and Medicare Advantage enrollees in the United States,¹¹ consisting of longitudinal health information for more than 100 million enrollees in the past 20 years. The data cover domains for enrollee information (sex, age, dates of eligibility, census region) and medical claims (including *International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* diagnosis codes, *ICD-9-CM* procedure codes, *Current Procedural Terminology*, version 4 procedure codes, Healthcare Common Procedure Coding System procedure codes, site of service codes, and provider specialty codes).¹² This study involved analysis of preexisting, deidentified data and was deemed exempt from institutional review board approval. Standardized methodologic reporting guidelines were followed (Reporting of Studies Conducted Using Observational Routinely Collected Health Data).¹³

Study Population

To identify the analytic cohort of emergency department (ED) visits for anaphylaxis from 2005 to 2014, we used 2 previously validated methods.¹⁴ Method 1 identified patients who had *ICD-9-CM* diagnosis codes for anaphylactic shock (995.60–995.69 and 995.0). Method 2 identified patients through an algorithm of *ICD-9-CM* codes of symptom combinations, including respiratory symptoms (respiratory failure or distress, dyspnea, asthma), cardiovascular symptoms (hypotension, syncope or collapse), gastrointestinal symptoms (allergic gastroenteritis or colitis, nausea, vomiting, abdominal pain), and mucocutaneous symptoms (angioedema, pruritus, flushing, urticaria, ocular, pharyngeal, or laryngeal edema). Outcomes examined included hospital or ICU admissions, endotracheal intubations, and near-fatal reactions. Hospital admissions included all patients admitted to a general medical ward and all patients admitted to an ICU. ICU admissions included admissions to a coronary care unit or medical ICU. Near-fatal reactions were defined by the occurrence of tracheostomy, respiratory arrest, or cardiac arrest.

Predictors examined in this study included cardiac disease, defined by the diagnoses hypertensive disease, coronary atherosclerosis, and congestive heart failure. Lung disease was defined as chronic airway obstruction and obstructive chronic bronchitis with acute exacerbation. Atopy was also evaluated based on the presence of asthma or eczema. Patients with prior visits to allergy/immunology specialists were also identified. All associated *ICD-9-CM* codes and *Current Procedural Terminology* codes used in this study are listed in eTable 1. Patients were required to have continuous medical insurance coverage for 12 months before the index event (anaphylaxis-related ED visit); those who did not were excluded. Those with census region documented as other ($n = 4$) or unknown ($n = 18$) also were excluded from the cohort.

Statistical Analysis

Patient characteristics were summarized as number (percentage). We calculated calendar year-, age-, and sex-specific and overall age- and sex-adjusted rates by using the number of ED visits for anaphylaxis as the numerator and number of all-cause ED visits as the denominator. Multivariable logistic regression was used to identify variables that were independently associated with severe anaphylaxis.¹⁵ To calculate odds ratios (ORs), reference groups were

defined by age (18–34 years), census regions (Midwest), and trigger (unspecified). Bivariate and multivariable analyses were adjusted for year of ED visit by including it in the model as 2-year increments (2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014) to account for any potential changes in clinical practice that could have occurred during the study period. Results are reported as ORs and 95% confidence intervals (CIs). All significance tests were 2-sided; $P < .01$ was considered statistically significant. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute Inc, Cary, North Carolina). To assess for potential differences between cohorts obtained via the different methods described above, a sensitivity analysis was performed including only those identified by method 1.

Results

During the 10-year study period, we identified 38,695 ED visits for anaphylaxis (Fig 1). Among these patients, 4,473 (11.6%) had any outcome of admission, intubation, or near-fatal reaction, alone or in combination. Specifically, 4,431 patients (11.5%) had severe anaphylaxis requiring hospitalization, 2,057 (5.3%) were admitted to the ICU, 567 (1.5%) required endotracheal intubation, and 174 (0.45%) had a near-fatal event (eTable 2).

Composite Outcome: Any Hospital Admission, ICU Admission, Intubation, or Near-Fatal Reaction

On multivariable analysis, predictors of any hospital admission, ICU admission, intubation, or near-fatal reaction included age of 65 years or older (OR, 3.15; 95% CI, 2.88–3.44; $P < .001$), medication as a trigger (OR, 1.50; 95% CI, 1.38–1.63; $P < .001$), and the presence of cardiac disease (OR, 1.56; 95% CI, 1.50–1.63; $P < .001$) or lung disease (OR, 1.23; 95% CI, 1.16–1.30; $P < .001$) (Table 1). Factors associated with decreased odds of any outcome were young age (0–4 years: OR, 0.69; 95% CI, 0.59–0.80; $P < .001$; 5–17 years: OR, 0.72; 95% CI, 0.65–0.80; $P < .001$), triggers including food (OR, 0.80; 95% CI, 0.73–0.87; $P < .001$) and venom (OR, 0.66; 95% CI, 0.56–0.76; $P < .001$), and a history of asthma (OR, 0.93; 95% CI, 0.89–0.97; $P < .001$). Having eczema and having an allergy/immunology consultation within 12 months before the ED visit were associated with decreased odds of severe anaphylaxis on bivariate analysis (eTable 3) but not on multivariable analysis (Table 1).

ICU Admission

Factors associated with increased odds of ICU admission on multivariable analysis were similar to the factors associated with the composite severe anaphylaxis outcome and included older age (35–64 years: OR, 1.27; 95% CI, 1.12–1.45; $P < .001$; ≥ 65 years: OR, 5.35; 95% CI, 4.63–6.19; $P < .001$) and the presence of cardiac (OR, 1.69; 95% CI, 1.59–1.80; $P < .001$) or lung disease (OR, 1.21; 95% CI, 1.12–1.30; $P < .001$) (Table 1). A history of asthma was associated with decreased odds of ICU admission on multivariable analysis (OR, 0.88; 95% CI, 0.82–0.93; $P < .001$). Young patients (< 18 years) were less likely to be admitted to the ICU (0–4 years: OR, 0.34; 95% CI, 0.24–0.49; $P < .001$; 5–17 years: OR, 0.56; 95% CI, 0.45–0.68; $P < .001$), as were patients with venom-related anaphylaxis (OR, 0.68; 95% CI, 0.55–0.85; $P < .001$) (Table 1). Eczema and allergy/immunology consultation 12 months before the ED visit were associated with a decreased odds of ICU admission on bivariate analysis (eTable 3) but were not significant on multivariable analysis (Table 1).

Endotracheal Intubation

On multivariable analysis, older age (≥ 65 years: OR, 5.62; 95% CI, 4.04–7.83; $P < .001$) and history of cardiac (OR, 2.14; 95% CI, 1.86–2.45; $P < .001$) or lung disease (OR, 1.21; 95% CI, 1.08–1.36;

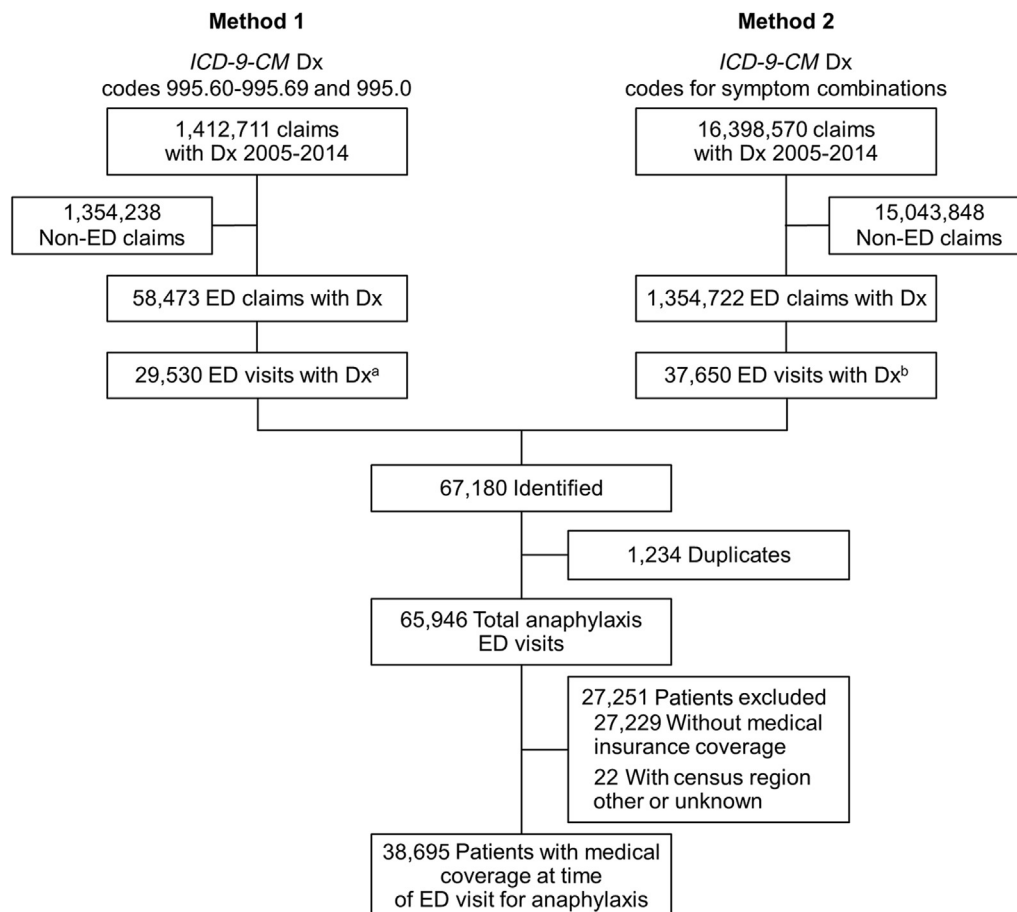


Figure 1. Flowchart of cohort identification. Dx, diagnosis; ED, emergency department; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*. Adapted with permission from Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Increasing emergency department visits for anaphylaxis, 2005–2014. *J Allergy Clin Immunol Pract*. 2017;5:171–175. ^aOf 58,473 claims, only 29,530 represented unique visits. ^bOf 1,354,722 claims, only 37,650 represented unique visits.

$P < .001$) were associated with increased odds of endotracheal intubation (Table 1). Factors that were associated with decreased odds of endotracheal intubation on multivariable analysis were venom as trigger (OR, 0.25; 95% CI, 0.11–0.60; $P = .002$) and history of asthma (OR, 0.84; 95% CI, 0.75–0.95; $P = .005$).

Near-Fatal Reaction

Age of 65 years or older (OR, 6.71; 95% CI, 3.85–11.71; $P < .001$) and history of cardiac disease (OR, 1.49; 95% CI, 1.22–1.83; $P < .001$) were associated with higher odds of a near-fatal reaction on multivariable analysis (Table 1). Allergy/immunology consult 12 months before the ED visit was associated with decreased odds of near-fatal complications on bivariate analysis, but the association was lost on multivariable analysis (eTable 3 and Table 1).

Sensitivity Analyses

In the sensitivity analysis of only patient visits identified by method 1 (anaphylaxis-specific codes), the findings were similar, with patients younger than 18 years having lower odds of severe anaphylaxis and patients older than 65 years having greater odds compared with patients aged 18 to 34 years (eTable 4). In addition, food and venom as triggers were associated with decreased odds of severe anaphylaxis, and medication was associated with increased odds of severe anaphylaxis. Cardiac and lung disease were also associated with increased odds of severe anaphylaxis. In contrast to the full analysis, asthma was associated with increased odds of severe anaphylaxis (OR, 1.13; 95% CI, 1.06–1.22; $P < .001$), whereas

an allergy/immunology visit within 12 months prior was associated with decreased odds of severe anaphylaxis (OR, 0.87; 95% CI, 0.79–0.95; $P = .03$). In addition, the Northeast census region was no longer associated with increased odds of severe anaphylaxis.

Furthermore, to account for potential bias by excluding those without a full year of insurance, we conducted follow-up analysis on the entire cohort, including all patients regardless of insurance coverage. Associations were similar to those found among patients with a full year of continuous medical coverage before the index ED visit (eTable 4).

Discussion

We studied more than 38,000 ED visits for anaphylaxis to examine risk factors associated with severe anaphylaxis, defined as anaphylaxis resulting in hospital or ICU admission, requiring endotracheal intubation, or meeting criteria for a near-fatal reaction. To our knowledge, this is one of the largest cohort studies to comprehensively analyze predictors of severe anaphylaxis. Overall, age of 65 years or older, medication as a trigger, and presence of cardiac and lung disease were associated with a higher likelihood of having severe anaphylaxis.

In this study, older patients (≥ 65 years) and those with cardiac and lung disease were more likely to be admitted to the ICU, to be intubated, or to have near-fatal outcomes. Previous studies^{15–18} agree that older patients with anaphylaxis have an increased likelihood of hospital admission. Although not examined in this study, older age has also been associated with greater odds of fatal anaphylaxis.¹⁹ Older age and the presence of multiple comorbid

Table 1Multivariable Predictors of Severe Anaphylaxis Requiring Hospital Admission, ICU Admission, or Intubation or Being a Near-Fatal Reaction^a

Category ^b	Any hospital admission, ICU admission, intubation, or near-fatal reaction (n = 4,473)		Hospital admission ^c (n = 4,431)		ICU admission ^d (n = 2,057)		Intubation ^e (n = 567)		Near-fatal reaction ^f (n = 174)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, y										
0–4	0.69 (0.59–0.80)	<.001	0.69 (0.60–0.81)	<.001	0.34 (0.24–0.49)	<.001	0.38 (0.15–0.97)	.04	0.30 (0.06–1.48)	.14
5–17	0.72 (0.65–0.80)	<.001	0.72 (0.66–0.80)	<.001	0.56 (0.45–0.68)	<.001	0.52 (0.30–0.90)	.02	0.54 (0.24–1.25)	.15
18–34	Reference		Reference		Reference		Reference		Reference	
35–64	0.96 (0.90–1.03)	.24	0.96 (0.89–1.02)	.19	1.27 (1.12–1.45)	<.001	1.32 (0.97–1.80)	.08	1.74 (1.04–2.90)	.03
≥65	3.15 (2.88–3.44)	<.001	3.12 (2.85–3.42)	<.001	5.35 (4.63–6.19)	<.001	5.62 (4.04–7.83)	<.001	6.71 (3.85–11.71)	<.001
Female sex	0.96 (0.93–1.00)	.04	0.97 (0.93–1.00)	.04	0.95 (0.90–0.99)	.02	1.07 (0.97–1.17)	.16	0.88 (0.76–1.03)	.10
Census region										
Midwest	Reference		Reference		Reference		Reference		Reference	
Northeast	1.15 (1.07–1.24)	<.001	1.16 (1.08–1.25)	<.001	0.92 (0.82–1.02)	.12	0.89 (0.72–1.09)	.27	0.60 (0.38–0.95)	.03
South	0.90 (0.86–0.95)	<.001	0.90 (0.86–0.95)	<.001	0.94 (0.88–1.02)	.12	0.99 (0.86–1.14)	.91	1.21 (0.94–1.56)	.15
West	0.90 (0.83–0.97)	.009	0.89 (0.82–0.97)	.005	1.05 (0.94–1.18)	.37	0.99 (0.79–1.24)	.91	1.03 (0.68–1.54)	.90
Trigger										
Unspecified	Reference		Reference		Reference		Reference		Reference	
Food	0.80 (0.73–0.87)	<.001	0.80 (0.73–0.87)	<.001	1.02 (0.90–1.16)	.74	1.36 (0.94–1.97)	.11	0.82 (0.51–1.33)	.43
Venom	0.66 (0.56–0.76)	<.001	0.64 (0.55–0.75)	<.001	0.68 (0.55–0.85)	<.001	0.25 (0.11–0.60)	.002	0.82 (0.41–1.64)	.58
Medication	1.50 (1.38–1.63)	<.001	1.51 (1.39–1.64)	<.001	1.03 (0.91–1.17)	.64	1.16 (0.81–1.65)	.42	0.91 (0.60–1.40)	.68
Cardiac disease	1.56 (1.50–1.63)	<.001	1.57 (1.50–1.64)	<.001	1.69 (1.59–1.80)	<.001	2.14 (1.86–2.45)	<.001	1.49 (1.22–1.83)	<.001
Asthma	0.93 (0.89–0.97)	<.001	0.93 (0.89–0.97)	<.001	0.88 (0.82–0.93)	<.001	0.84 (0.75–0.95)	.005	1.03 (0.84–1.25)	.79
Lung disease	1.23 (1.16–1.30)	<.001	1.23 (1.16–1.30)	<.001	1.21 (1.12–1.30)	<.001	1.21 (1.08–1.36)	<.001	1.09 (0.88–1.34)	.44
Eczema	0.98 (0.93–1.03)	.51	0.98 (0.93–1.03)	.50	0.94 (0.87–1.02)	.14	1.00 (0.88–1.15)	.96	0.97 (0.76–1.25)	.83
Allergy visit (prior 12 mo)	0.96 (0.90–1.01)	.13	0.96 (0.91–1.02)	.19	0.98 (0.90–1.08)	.71	0.83 (0.68–1.01)	.06	0.64 (0.42–0.97)	.03

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

^aMultivariable analysis was adjusted for year of visit.^bReference group of age 18 to 34 years was chosen for comparative purposes based on a prior study.¹⁵ Midwest and unspecified trigger reference groups were chosen arbitrarily for the purpose of calculating an OR.^cHospital admissions included all patients admitted to a general medical ward and to an ICU.^dICU admissions included admissions to a coronary care unit or medical ICU.^eIntubation included those who underwent endotracheal intubation.^fNear-fatal reactions were defined by the occurrence of tracheostomy, respiratory arrest, or cardiac arrest.

conditions, including lung and cardiac disease, may be stronger predictors of severe reactions because they may imply impaired physiologic compensatory mechanisms and an inability to tolerate anaphylaxis-related complications, such as hypotension and hypoxia.^{4,7,19} Moreover, particularly for patients with coronary artery disease, the odds of severe anaphylaxis may be higher because of an increased load of cardiac mast cells and underlying coronary stenosis, leading to a higher risk of myocardial hypoxia.^{17,19} In addition, patients with cardiac disease are often taking antihypertensive medications, particularly β -blockers and angiotensin-converting enzyme inhibitors, which have also been associated with direct mast cell priming effects.²⁰

Medication as a trigger was associated with increased odds of the composite outcome of severe anaphylaxis on multivariable analysis. Clark et al¹⁵ used a stricter definition for severe anaphylaxis—cardiorespiratory arrest or resuscitative cardiopulmonary interventions—and found that patients with medicine as a trigger were more than twice as likely to have severe anaphylaxis. Previous studies have reported that medications are the most common cause of fatal anaphylaxis in the United States²¹ and elsewhere.^{8,22} Anaphylactic reactions to medications can escalate quickly—a median time to respiratory or cardiac arrest of only 5 minutes compared with 30 minutes for foods and 15 minutes for venom in one study.²³ Other studies found that rates of fatalities attributable to medication-related anaphylaxis increased by more than 300% in the past decade in Australia⁸ and that, in the United States, antibiotics accounted for nearly 40% of the cases if a trigger could be identified.²¹ These findings highlight the importance of proper management of drug allergies.

Of interest, multivariable analysis found that asthma was less likely to be a predictor of hospital admission, ICU admission, and endotracheal intubation. This finding is surprising because asthma

is considered a risk factor for fatal events by many consensus guidelines.^{24,25} Retrospective studies, particularly observational studies of fatal food-induced anaphylaxis,^{26,27} have reported an association between asthma and anaphylaxis fatality, but recent literature suggests that asthma itself is not a strong predictor of more severe anaphylaxis. Clark et al¹⁵ did not find asthma to be a significant risk factor for severe anaphylaxis. Moreover, in the literature on pediatric food-induced anaphylaxis, up to 50% of food allergic children have asthma, but only a few will have a fatal food-induced anaphylactic reaction.^{28,29} Studies of fatal and near-fatal reactions to allergen immunotherapy suggest that suboptimal asthma control, rather than just the presence of asthma, may increase a patient's likelihood of having severe anaphylaxis.^{30,31} Our sensitivity analysis, including only patients identified by anaphylaxis-specific ICD-9-CM codes, demonstrated increased odds of severe anaphylaxis among patients with asthma. We hypothesize that the cases identified with these ICD-9-CM codes, which are for anaphylactic shock, most likely represent the most serious cases of anaphylaxis, and in this subset, asthma may have a more substantial effect. These findings require further studies to examine the complex interactions between anaphylaxis and asthma.

Eczema was associated with decreased odds of hospital and ICU admission on bivariate analysis but not on multivariable analysis. Results regarding eczema as a predictor of anaphylaxis are variable and depend on the type of anaphylaxis. For example, atopy, including eczema, is a risk factor for food allergies and food-induced anaphylaxis.³² Moreover, in studies of food-induced anaphylaxis, eczema and coexisting atopic disease have been associated with a greater risk of life-threatening reactions.^{32,33} In a previous study by Summers et al³³ that examined risk factors for peanut and tree nut anaphylaxis, an altered level of consciousness was more likely in those with severe eczema (OR, 3.1). In contrast,

in studies of medication-induced anaphylaxis, eczema and atopic disease were not significant predictors of severe anaphylaxis.³⁴ Additional studies are needed to further define the effects of eczema on the overall risk of severe anaphylaxis.

Allergy/immunology consultation within 12 months before the ED visit was associated with decreased hospital admissions and ICU admissions on bivariate but not multivariable analysis. In our sensitivity analysis, however, allergy/immunology consultation was associated with decreased odds of severe anaphylaxis; thus, the effect of prior allergy/immunology consultation may be significant in this subgroup. Education provided during the allergy/immunology consultation may result in patients being more likely to use their epinephrine autoinjector and to seek urgent medical attention, which may improve outcomes and reduce the need for admission. Furthermore, these patients may be better prepared for future reactions, which results in the patient and/or practitioner feeling more confident with dismissal directly from the ED. Clark et al¹⁵ found that an allergy/immunology visit before the index event was associated with a decreased odds of near-fatal outcomes. Campbell et al³⁵ reported that up to 35% of patients with anaphylaxis seen in the ED had an alteration in the diagnosis or suspected trigger after allergy/immunology consultation. Post-ED anaphylaxis follow-up with an allergy/immunology specialist is recommended by current guidelines.^{24,25} Further studies are needed similar to the study by Messina et al,³⁶ which identified effective interventions to promote specialty follow-up after ED discharge.

In our study cohort, the odds of severe anaphylaxis were higher in the Northeast (OR, 1.15) and lower in the South (OR, 0.90) relative to the Midwest, which suggests that geographic region may be a factor. However, in our sensitivity analysis, the odds of severe anaphylaxis were no longer increased among patients in the Northeast census region. Prior studies have reported that areas with less year-round sunlight had increased epinephrine prescription rates^{37,38} and higher rates of ED visits for acute allergic reactions.³⁹ This is frequently explained in terms of the vitamin D anaphylaxis hypothesis—vitamin D is often insufficient in patients with food allergy, atopic dermatitis, and asthma.⁴⁰ Vitamin D has broad immunomodulatory effects impairing T-cell proliferation⁴¹ and mast cell stabilization properties.⁴² Additional studies are needed to verify our findings and further define the role of vitamin D in allergic disease.

The strengths of our study are the use of real-world data outside clinical trials, large sample size, inclusion of multiple academic and nonacademic institutions that might differ in practice patterns, and a rigorous method during the selection of patients and statistical analysis. Limitations include those inherent to administrative claims data, including use of data not created or collected to answer the research question; potential for coding errors, such as undercoding comorbid conditions or outcomes; the possibility of underreporting cases (we could not validate diagnoses with medical record review); and unmeasured confounding of observational studies. In addition, other variables that we could not account for, including the use and timing of epinephrine, along with corticosteroids, may further explain our findings. In addition, many cases had an unspecified trigger; thus, it is unclear whether the trigger was unknown after evaluation or was not specified in the diagnosis. In addition, our sample is large and diverse in age and geographic representation but is limited to privately insured and Medicare Advantage enrollees. The exclusion of those without health insurance thus represents a limitation of our study because it is not a true national sample. It is unclear whether the inclusion of such patients would have changed our findings. Finally, nearly half of the cases were from the Southern United States, with a minority in the Northeast region; this finding reflects the geographic distribution of patients in the database but may underestimate rates of anaphylaxis because anaphylaxis rates

are higher in more northerly latitudes.^{38,39,43} Although population-level studies such as this have some limitations, they are essential in studying the epidemiology of anaphylaxis. We agree with Turner and Campbell⁴⁴ in that improvements are needed in our current abilities to accurately gather and analyze population-level data. Perhaps movement toward a national health claims database, similar to that reported by Yang et al,⁴⁵ which covers 97.9% of the entire Korean population, would assist in improving the accuracy of current national studies.

In conclusion, in this large contemporary cohort, more than 10% of patients seen in the ED with anaphylaxis had severe anaphylaxis and 0.45% had a near-fatal reaction. Findings of our study highlight the importance of anaphylaxis prevention in the elderly population and others with multiple comorbid conditions and high medication burden, which were all significantly associated with severe anaphylaxis. Although only a few allergic reactions will be life-threatening, efforts to identify factors related to severe anaphylactic reactions are important to guide future approaches in management and prevention. Such studies will help target those who would most benefit from interventions, including disease-modifying therapies, such as epicutaneous and oral immunotherapy for food allergies currently in development,⁴⁶ and will provide further insight into appropriate resource allocation.

Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anaai.2017.07.014>.

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Supplementary Data

eTable 1

Professional Claims

Description of diagnosis	Professional claims
Triggers	
Food	693.10, 995.6x, and 995.7
Medication	693.0, 995.2x, 995.4, E930.x, and E931.x
Venom	989.5, E905.3, E905.5, E905.8, and E905.9
Other	Not categorized in above 3 groups
Cardiac disease	
Hypertensive disease	401.x, 402.xx, 404.xx, 405.xx
Coronary atherosclerosis	414.00–414.05
Congestive heart failure	428.x
Lung disease	
Chronic airway obstruction	496
Obstructive chronic bronchitis with acute exacerbation	491.21
Asthma	493.xx except 493.93
Eczema	691.8, 692.xx except 692.97
Allergy/immunology visit before index event	CPT codes 99201–99205, 99211–99215, and 99241–99245
ICU admission	
Intensive care	Revenue codes 20x
Coronary care	Revenue codes 210, 211, 212, 214, 219
Near-fatal reaction	
Tracheostomy	31.1; CPT codes 31603, 31605
Respiratory arrest	799.1
Cardiac arrest	427.5
Endotracheal intubation	96.04, 96.05; CPT code 31500

Abbreviations: CPT, *Current Procedural Terminology*; ICU, intensive care unit.**eTable 2**

Demographic and Clinical Characteristics of Patients Admitted to the Hospital or ICU, Intubated, or With Near-Fatal Outcomes

Category	All patients (N = 38,695)	Outcome				
		Any admission, intubation, or near-fatal reaction (n = 4,473)	Hospital admission (n = 4,431)	ICU admission (n = 2,057)	Intubation (n = 567)	Near-fatal reaction (n = 174)
Age, y						
0–4	2,871 (7.4)	133 (3.0)	132 (3.0)	20 (1.0)	3 (0.5)	1 (0.6)
5–17	6,950 (18.0)	356 (8.0)	354 (8.0)	82 (4.0)	11 (1.9)	5 (2.9)
18–34	8,036 (20.8)	466 (10.4)	460 (10.4)	158 (7.7)	24 (4.2)	7 (4.0)
35–64	17,205 (44.5)	2,069 (46.3)	2,047 (46.2)	862 (41.9)	206 (36.3)	75 (43.1)
≥65	3,633 (9.4)	1,449 (32.4)	1,438 (32.5)	935 (45.5)	323 (57.0)	86 (49.4)
Sex						
Female	22,287 (57.6)	2,640 (59.0)	2,616 (59.0)	1,204 (58.5)	361 (63.7)	96 (55.2)
Male	16,408 (42.4)	1,833 (41.0)	1,815 (41.0)	853 (41.5)	206 (36.3)	78 (44.8)
ED visit year						
2005–2006	4,803 (12.4)	547 (12.2)	540 (12.2)	205 (10.0)	45 (7.9)	21 (12.1)
2007–2008	6,149 (15.9)	760 (17.0)	753 (17.0)	281 (13.7)	51 (9.0)	23 (13.2)
2009–2010	7,167 (18.5)	899 (20.1)	892 (20.1)	384 (18.7)	107 (18.9)	28 (16.1)
2011–2012	9,456 (24.4)	1,070 (23.9)	1,061 (23.9)	530 (25.8)	165 (29.1)	47 (27.0)
2013–2014	11,120 (28.7)	1,197 (26.8)	1,185 (26.7)	657 (31.9)	199 (35.1)	55 (31.6)
Census region						
Northeast	5,265 (13.6)	646 (14.4)	644 (14.5)	252 (12.3)	66 (11.6)	12 (6.9)
South	17,806 (46.0)	2,036 (45.5)	2,020 (45.6)	955 (46.4)	271 (47.8)	89 (51.1)
West	5,378 (13.9)	482 (10.8)	473 (10.7)	229 (11.1)	52 (9.2)	16 (9.2)
Midwest	10,246 (26.5)	1,309 (29.3)	1,294 (29.2)	621 (30.2)	178 (31.4)	57 (32.8)
Trigger						
Food	10,464 (27.0)	591 (13.2)	582 (13.1)	249 (12.1)	45 (7.9)	14 (8.0)
Medication	4,661 (12.0)	814 (18.2)	807 (18.2)	296 (14.4)	60 (10.6)	20 (11.5)
Venom	1,596 (4.1)	118 (2.6)	114 (2.6)	53 (2.6)	3 (0.5)	5 (2.9)
Unspecified	21,974 (56.8)	2,950 (66.0)	2,928 (66.1)	1,459 (70.9)	459 (81.0)	135 (77.6)
Charlson Comorbidity Index						
0	19,665 (50.8)	1,371 (30.7)	1,357 (30.6)	511 (24.8)	106 (18.7)	35 (20.1)
1	8,133 (21.0)	770 (17.2)	757 (17.1)	332 (16.1)	79 (13.9)	31 (17.8)
≥2	10,897 (28.2)	2,332 (52.1)	2,317 (52.3)	1,214 (59.0)	382 (67.4)	108 (62.1)
Comorbid conditions						
Cardiac disease	11,006 (28.4)	2,705 (60.5)	2,685 (60.6)	1,480 (71.9)	478 (84.3)	129 (74.1)
Asthma	9,619 (24.9)	957 (21.4)	944 (21.3)	386 (18.8)	99 (17.5)	35 (20.1)
Lung disease	1,892 (4.9)	622 (13.9)	617 (13.9)	357 (17.4)	124 (21.9)	31 (17.8)
Eczema	5,643 (14.6)	546 (12.2)	541 (12.2)	221 (10.7)	64 (11.3)	18 (10.3)
Allergy visit (prior 12 mo)	5,694 (14.7)	417 (9.3)	416 (9.4)	159 (7.7)	29 (5.1)	6 (3.4)

Abbreviations: ED, emergency department; ICU, intensive care unit.

eTable 3Bivariate Predictors of Severe Anaphylaxis Requiring Hospital Admission, ICU Admission, or Intubation or Being a Near-Fatal Reaction^a

Category	Any admission, intubation, or near-fatal reaction (n = 4,473)		Hospital admission (n = 4,431)		ICU admission (n = 2,057)		Intubation (n = 567)		Near-fatal reaction (n = 174)	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, y										
0–4	0.45 (0.39–0.52)	<.001	0.45 (0.39–0.52)	<.001	0.22 (0.16–0.32)	<.001	0.18 (0.07–0.46)	<.001	0.19 (0.04–0.91)	.04
5–17	0.50 (0.45–0.55)	<.001	0.50 (0.46–0.55)	<.001	0.38 (0.31–0.46)	<.001	0.28 (0.16–0.48)	<.001	0.38 (0.17–0.87)	.02
18–34	Reference		Reference		Reference		Reference		Reference	
35–64	1.27 (1.19–1.34)	<.001	1.26 (1.19–1.34)	<.001	1.68 (1.49–1.89)	<.001	2.14 (1.60–2.86)	<.001	2.33 (1.43–3.81)	<.001
≥65	6.15 (5.73–6.59)	<.001	6.13 (5.72–6.58)	<.001	11.02 (9.78–12.43)	<.001	17.20 (12.95–22.86)	<.001	12.93 (7.94–21.05)	<.001
Female sex	1.03 (1.00–1.07)	.04	1.03 (1.00–1.07)	.04	1.02 (0.98–1.07)	.38	1.14 (1.04–1.24)	.003	0.95 (0.82–1.11)	.52
Census region										
Midwest	Reference		Reference		Reference		Reference		Reference	
Northeast	1.10 (1.03–1.18)	.006	1.11 (1.04–1.19)	.003	0.94 (0.85–1.04)	.24	0.94 (0.77–1.14)	.52	0.61 (0.39–0.96)	.03
South	1.02 (0.97–1.07)	.52	1.02 (0.97–1.07)	.45	1.06 (0.99–1.14)	.10	1.14 (1.00–1.30)	.06	1.35 (1.05–1.74)	.02
West	0.78 (0.72–0.84)	<.001	0.77 (0.71–0.83)	<.001	0.83 (0.75–0.93)	<.001	0.72 (0.58–0.90)	.003	0.80 (0.54–1.20)	.28
Trigger										
Unspecified	Reference		Reference		Reference		Reference		Reference	
Food	0.53 (0.49–0.58)	<.001	0.54 (0.49–0.58)	<.001	0.54 (0.48–0.61)	<.001	0.63 (0.43–0.90)	.01	0.41 (0.26–0.66)	<.001
Venom	0.71 (0.62–0.82)	<.001	0.70 (0.60–0.81)	<.001	0.77 (0.62–0.95)	.01	0.27 (0.12–0.64)	.003	0.97 (0.49–1.91)	.92
Medication	1.89 (1.75–2.04)	<.001	1.91 (1.76–2.06)	<.001	1.51 (1.35–1.70)	<.001	1.89 (1.33–2.68)	<.001	1.32 (0.87–2.01)	.19
Charlson Comorbidity Index										
0	Reference		Reference		Reference		Reference		Reference	
1	0.81 (0.77–0.86)	<.001	0.81 (0.76–0.85)	<.001	0.82 (0.75–0.88)	<.001	0.79 (0.67–0.93)	.004	0.94 (0.72–1.22)	.63
≥2	2.11 (2.03–2.21)	<.001	2.12 (2.03–2.22)	<.001	2.40 (2.26–2.55)	<.001	2.92 (2.59–3.29)	<.001	2.45 (2.00–3.01)	<.001
Cardiac disease	2.19 (2.12–2.26)	<.001	2.19 (2.12–2.26)	<.001	2.70 (2.57–2.84)	<.001	3.75 (3.35–4.20)	<.001	2.70 (2.28–3.20)	<.001
Asthma	0.90 (0.86–0.93)	<.001	0.89 (0.86–0.93)	<.001	0.83 (0.78–0.88)	<.001	0.80 (0.71–0.89)	<.001	0.87 (0.72–1.05)	.15
Lung disease	2.05 (1.95–2.15)	<.001	2.05 (1.94–2.15)	<.001	2.19 (2.06–2.33)	<.001	2.40 (2.17–2.66)	<.001	2.07 (1.70–2.51)	<.001
Eczema	0.89 (0.85–0.93)	<.001	0.89 (0.85–0.93)	<.001	0.83 (0.78–0.89)	<.001	0.86 (0.76–0.98)	.03	0.82 (0.64–1.05)	.11
Allergy visit (prior 12 mo)	0.75 (0.71–0.79)	<.001	0.75 (0.72–0.80)	<.001	0.69 (0.63–0.74)	<.001	0.56 (0.46–0.67)	<.001	0.45 (0.30–0.68)	<.001

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

^aBivariate analysis was adjusted for time.**eTable 4**

Multivariable Predictors of Severe Anaphylaxis Requiring Hospital Admission, ICU Admission, or Intubation or Being a Near-Fatal Reaction Based on Patients Identified by Method 1 Only and Among Patients With and Without 1 Full Year of Continuous Medical Coverage Before the Index ED Visit

Category	Patients identified by method 1 (Anaphylaxis-specific ICD-9-CM Codes) only		Patients with and without 1 year of continuous medical insurance before index ED visit	
	OR (95% CI)	P value	OR (95% CI)	P value
Age, y				
0–4	0.76 (0.63–0.91)	.003	0.79 (0.71–0.88)	<.001
5–17	0.80 (0.70–0.91)	.001	0.69 (0.63–0.75)	<.001
18–34	Reference	Reference	Reference	Reference
35–64	0.89 (0.80–0.98)	.02	1.05 (1.00–1.11)	.045
≥65	3.08 (2.65–3.58)	<.001	2.75 (2.58–2.92)	<.001
Female sex	1.02 (0.96–1.08)	.003	0.96 (0.94–0.99)	.003
Census region				
Midwest	Reference	Reference	Reference	Reference
Northeast	1.03 (0.91–1.16)	.66	1.09 (1.03–1.15)	.003
South	0.89 (0.81–0.97)	.008	0.88 (0.85–0.92)	<.001
West	0.98 (0.87–1.12)	.80	1.02 (0.97–1.07)	.47
Trigger				
Unspecified	Reference	Reference	Reference	Reference
Food	0.77	<.001	0.81 (0.76–0.87)	<.001
Venom	0.56	<.001	0.64 (0.57–0.72)	<.001
Medication	1.84 (1.57–2.16)	<.001	1.41 (1.33–1.50)	<.001
Cardiac disease	1.44 (1.35–1.55)	<.001	1.44 (1.40–1.49)	<.001
Asthma	1.13 (1.06–1.22)	<.001	0.92 (0.89–0.95)	<.001
Lung disease	1.41 (1.26–1.58)	<.001	1.21 (1.16–1.26)	<.001
Eczema	1.00 (0.91–1.08)	.91	0.96 (0.92–1.00)	.06
Allergy visit (prior 12 mo)	0.87 (0.79–0.95)	.003	0.94 (0.90–0.99)	.01

Abbreviations: CI, confidence interval; ED, emergency department; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICU, intensive care unit; OR, odds ratio.