
Asthma and the prospective risk of anaphylactic shock and other allergy diagnoses in a large integrated health care delivery system

Carlos Iribarren, MD, PhD, MPH*; Irina V. Tolstykh, MS*; Mary K. Miller, MS†; and Mark D. Eisner, MD, MPH‡

Background: The association between asthma and anaphylaxis remains poorly understood.

Objective: To ascertain, in a managed care organization in northern California, the association of asthma and asthma severity with future risk of anaphylactic shock and other selected allergy diagnoses.

Methods: Using electronic data and validated algorithms, we assembled a cohort of 526,406 patients who met the criteria for asthma between 1996 and 2006 and a referent cohort (with no utilization for asthma) individually matched on age, sex, and race/ethnicity. In each cohort, 54% of patients were female and 55% were white; their mean (SD) age was 24 (20) years. The main outcome measures were anaphylactic shock (caused by an adverse food reaction, caused by serum, or other/idiopathic), allergic urticaria, anaphylaxis after sting(s), and angioedema.

Results: The incidence of anaphylactic shock was 109.0 per 100,000 person-years in the asthma cohort and 19.9 per 100,000 person-years in the referent cohort. After adjustment for age, sex, race/ethnicity, comorbidities, and immunotherapy, asthma was associated with a 5.2-fold (95% confidence interval, 4.7- to 5.6-fold) increased hazard of anaphylactic shock. Asthma was also significantly associated with an increased risk of the 3 selected allergy diagnoses, with hazard ratios of 1.4 to 1.9. A significant trend by severity of asthma was apparent for food-related and other/idiopathic anaphylactic shock and for anaphylaxis after sting(s).

Conclusions: In this insured population, asthma was prospectively associated with increased risk of anaphylactic shock and other allergy diagnoses. However, the effect of asthma severity was not consistent across outcome measures.

Ann Allergy Asthma Immunol. 2010;104:371–377.

INTRODUCTION

Although it has reached a plateau, the prevalence of asthma has doubled in the United States during the past 2 decades.¹ Moreover, national surveillance data² indicate that the severity of asthma is also increasing, as evidenced by rising rates of emergency department admissions and mortality through the mid-1990s.

Although not all asthma is IgE mediated, it is a common clinical observation that asthmatic patients are prone to allergic reactions.^{3–6} However, the incidence of anaphylaxis-related events and other allergy diagnoses in patients with asthma has not been systematically examined at the population level across sex, age, and racial/ethnic groups. Furthermore, the impact of asthma severity on the risk of anaphylaxis and allergy remains poorly understood. The primary objective of this study in a managed care setting was 2-fold: first, to ascertain the incidence of anaphylactic shock and other selected allergy diagnoses in patients with asthma and in a matched control sample of asthma-free individuals and, second, to elucidate the association of asthma and asthma severity with future risk of anaphylactic shock and other selected allergy diagnoses.

METHODS

Source Population and Study Design

Kaiser Permanente of Northern California (KPNC) has been in existence for approximately 50 years and comprises 16 hospitals and 38 ambulatory care facilities. Membership is stable, with less than 10% turnover annually overall and less than 3% to 5% in members 65 years and older or who have a chronic illness. Currently, KPNC cares for approximately 3.1 million members, and 17% of members are 65 years and older. The program delivers comprehensive inpatient and outpatient care to its members and captures many aspects of its care through use of its multiple comprehensive clinical and administrative databases. The KPNC population is not only ethnically but also socioeconomically diverse, and it is broadly representative of the Northern California population.⁷ By source of insurance coverage, the membership is 78.5%

Affiliations: * Division of Research, Kaiser Permanente, Oakland, California; † Genentech Inc, South San Francisco, California; ‡ Division of Occupational and Environmental Medicine and Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of California, San Francisco, California.

Disclosures: Authors have nothing to disclose.

Funding Sources: This study was supported by Genentech Inc.

Received for publication December 15, 2009; Received in revised form February 12, 2010; Accepted for publication March 7, 2010.

© 2010 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.03.004

commercial (mostly through employment), 11% Medicare, 2.5% MediCal and other Special Programs, and 8% self-pay.

We retrospectively identified a cohort of KPNC members with asthma (ie, the “asthma cohort”; $n=526,406$) and a comparable cohort of KPNC members without asthma (ie, the “referent cohort”; $n=526,406$) individually matched on age, sex, and race/ethnicity to the asthma cohort.

The inclusion and exclusion criteria for the asthma cohort, which included health care utilization between January 1, 1996, and December 31, 2006, have been used extensively^{8–10} and have been previously validated in the KPNC membership by means of medical record review.^{9,11} The inclusion criteria for the asthma cohort were all ages (with prespecified strata of 0–11, 12–18, 19–45, 46–64, and ≥ 65 years), active KPNC membership on the index date, and evidence of health care utilization for asthma. The latter included hospitalization with an *International Classification of Diseases, Ninth Revision* (ICD-9) primary discharge code 493.00 to 493.99 or a secondary code for asthma with a principal ICD-9 code for acute asthma-related respiratory conditions (pneumonia, influenza with pneumonia, acute upper respiratory tract infection, acute bronchitis and bronchiolitis, pulmonary collapse, respiratory failure, other pulmonary insufficiency, pneumothorax, and viral infection) or 2 or more outpatient or emergency department visits for asthma within a 12-month period. An additional entry criterion for the asthma cohort (in the absence of other health care utilization) was 2 or more prescriptions for an asthma medication during a 12-month period (inhaled β -agonists, inhaled corticosteroids, leukotriene modifiers, chromone medications, and combined inhaled corticosteroids and inhaled β -agonists). However, because of potential misclassification with chronic obstructive pulmonary disease in older patients, this medication-only criterion was not sufficient for adults 40 years and older. The exclusion criteria for the asthma cohort included utilization for chronic obstructive pulmonary disease (ICD-9 code 492 or 496) within 1 year before the index date. The index date was defined as the first date on which the entry criteria for the asthma cohort were met.

The referent cohort comprised health plan members with no utilization for asthma who were individually matched to patients in the asthma cohort on age, sex, and race/ethnicity. Furthermore, referent subjects were required to be active health plan member during the period where his or her matched asthmatic patient was a member, but the membership of the referent subject could have started before or lasted longer than the membership of the matched patient with asthma. Prevalent comorbidities (diabetes mellitus, cancer, coronary heart disease, ischemic stroke, heart failure, human immunodeficiency virus or AIDS, and hepatitis) dating back to 1980 were ascertained using relevant inpatient and outpatient codes. History of immunotherapy use during the same period was established using procedure codes representing administration of allergen immunotherapy by subcutaneous injection. We sought and obtained Kaiser Foundation Research Institute institutional review board approval for the

conduct of this study. Written consent for the use of data for research purposes was given by KPNC members when they joined the health plan.

Definition of Anaphylactic Shock and Related Allergy Diagnoses

We based the ascertainment of outcomes on the work of Bohlke et al.³ We searched for hospitalizations, ambulatory visits, and emergency department visits with ICD-9 codes 995.6 (anaphylactic shock caused by an adverse food reaction), 999.4 (anaphylactic shock caused by serum), and 995.0 (other anaphylactic shock). In addition, we also ascertained the incidence of other selected allergy-related diagnoses, including allergic urticaria (ICD-9 code 708.0), anaphylaxis after sting(s) (ICD-9 code 989.5), and angioneurotic edema (ICD-9 code 995.1).

Because of its idiopathic nature, we undertook a validation of the “other anaphylactic shock” ICD-9 code 995.0 (extreme nonfood allergy causing respiratory distress and vascular collapse). To this end, we randomly selected 120 medical records (60 from asthmatic patients and 60 from referent subjects) with the aforementioned code. Of these, 11 medical records were not available at the time of the review, leaving results from 109 records. Each medical record was abstracted by a trained medical record analyst using a standardized medical record review form. Each medical record abstraction form was then reviewed by a physician asthma specialist investigator (M.D.E.) using the criteria developed at the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium.¹² Each patient was characterized as having likely/probable, possible, a history of, or no anaphylactic shock. Of the 109 events reviewed, 57 (52%) were likely/probable, 22 (20%) were possible, 23 (21%) had a history of, and 7 (6%) were not anaphylactic shock events. The positive predictive values were 52% for likely/probable, 72% for likely/probable plus history of, and 93% for likely/probable plus possible plus history of anaphylactic shock. These estimates did not differ by asthma status (exact $P>.25$ for all). Estimation of sensitivity and specificity was not possible because we did not review medical records of patients with no anaphylactic shock events in the electronic databases. Of the 79 patients classified as having likely/probable anaphylactic shock, 65% were treated with epinephrine, 63% with corticosteroids, and 71% with antihistamines, and there were no differences in these percentages by asthma status. Of these 79 confirmed episodes, 27% had cutaneous, 15% had mucous membrane, 56% had respiratory, 22% had cardiovascular (ie, acute hypotensive episode), and 5% had gastrointestinal manifestations. A significantly higher proportion of patients without asthma had mucous membrane manifestations (26 of 42; 62%) compared with patients with asthma (1 of 37; 3%) (exact $P=.004$). Validation results by medical record review of the other codes performed in another database can be found in the recent work by Bohlke et al.³

Definitions of Asthma Severity

To define severe asthma, we implemented an algorithm based on validated indicators of asthma severity: hospitalization or intensive care unit admission for asthma (with or without endotracheal intubation) or a high-risk pharmacologic profile, defined as 1 or more of the following: dispensing of 3 or more oral corticosteroid prescriptions during the past year, dispensing of 1.4 or more short-acting β -agonist metered-dose inhalers per month for 3 or more months during the year before the index date, and high-level dispensing of inhaled corticosteroid inhalers during the year before the index date (highest quartile of dispensing).¹³

Statistical Analysis

Beginning at the index date for each participant, and separately for individuals in the asthma cohort and the referent cohort, we calculated the incidence rate per 100,000 person-years of anaphylactic shock events and other allergy diagnoses. For each outcome, individuals with a history of the corresponding event were excluded from the analysis. Right censoring was then applied at the first event, death, or discontinuation of health plan membership. To examine the association between asthma and the study outcomes, we used Cox proportional hazards models with asthma as the main independent variable. We first fit an age-, sex-, and race-adjusted model (model 1) and then a multivariate model with additional control for prevalent comorbidities and history of immunotherapy use (model 2). We performed a priori subgroup analyses of study outcomes stratifying by sex, race/ethnicity, and age and formally tested for interactions between asthma and these factors. To assess the potential modifying effect of asthma severity, we ran models with 2 separate main predictors, nonsevere asthma and severe asthma. Because the definition of asthma in patients younger than 40 years (which relied in some instances solely on pharmacy dispensing) was sensitive but not highly specific, we performed a secondary analysis requiring that all asthmatic patients had outpatient or inpatient health care utilization for asthma. Results of this analysis were consistent with those of the main analysis presented in this article (and tended to show somewhat stronger associations) (Supplementary Tables 1 and 2). All statistical analyses were performed using SAS version 9.13 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The asthma cohort was 54% female; in those with known race/ethnicity, the distribution was 55% white, with a substantive proportion being of minority background: 14% Asian, 13% Hispanic/Latino, 11% black, 6% mixed, 1% American Indian, and less than 1% Pacific Islander (Table 1). The mean patient age was 24 years; 38% were younger than 12 years and 5% were 65 years and older. By design, the referent cohort had the same sociodemographic characteristics. The asthma and referent cohorts had similar prevalences of diabetes, cancer, coronary heart disease, heart failure, ischemic stroke, hepatitis, and human immunodeficiency vi-

Table 1. Sociodemographic Characteristics and Comorbidities of the Asthma and Referent Cohorts

Characteristic	Asthma Cohort (n=526,406)	Referent Cohort (n=526,406)
Sex, No. (%)		
Female	285,182 (54)	285,182 (54)
Male	241,224 (46)	241,224 (46)
Race/ethnicity, No. (%)		
Asian	50,277 (10)	50,277 (10)
Black	38,780 (7)	38,780 (7)
Hispanic/Latino	47,040 (9)	47,040 (9)
Pacific Islander	48 (<1)	48 (<1)
Mixed	21,845 (4)	21,845 (4)
American Indian	2,985 (<1)	2,985 (<1)
White	199,313 (38)	199,313 (38)
Unknown	166,118 (32)	166,118 (32)
Age, mean (SD), y	24.2 (20.9)	24.4 (20.7)
Age, No. (%)		
0–11 y	198,335 (38)	199,397 (38)
12–18 y	62,528 (12)	61,786 (12)
19–45 y	173,627 (33)	173,196 (33)
46–64 y	65,674 (12)	66,065 (13)
≥65 y	26,242 (5)	25,962 (5)
Prevalent comorbidities, No. (%)		
Diabetes mellitus	13,796 (2.6)	11,807 (2.2)
Cancer	7,201 (1.4)	7,854 (1.5)
Coronary heart disease	10,473 (2.0)	8,084 (1.5)
Heart failure	2,846 (0.5)	1,485 (0.3)
Ischemic stroke	2,200 (0.4)	2,090 (0.4)
Hepatitis	1,724 (0.3)	1,668 (0.3)
HIV/AIDS	740 (0.14)	426 (0.08)
Immunotherapy use	5,006 (1)	965 (0.2)

Abbreviation: HIV, human immunodeficiency virus.

rus or AIDS. On the other hand, previous immunotherapy use was far more common in patients with asthma than in their counterparts without asthma.

During median follow-up of 5.2 years (interquartile range, 2.3–8.6 years) in asthmatic patients and 6.3 years (interquartile range, 3.3–9.3 years) in nonasthmatic individuals, there were 3,141 and 650 anaphylactic shock events of any type, respectively. When more than 1 event occurred, the average number of any anaphylactic shock events was 1.4 and 1.3 in the asthma and referent cohorts, respectively.

The rates of any anaphylactic shock by sex, asthma status, and age are presented in Figure 1. A peak in incidence was evident in individuals 19 to 45 years old and was more pronounced in patients with asthma and in women. Age-adjusted rates of any anaphylactic shock were consistently greater for the asthma cohort compared with the referent cohort across all race/ethnic groups (data not shown). The number of events and the corresponding rates of the specific types of anaphylactic shock and other allergy diagnoses are given in Table 2. All the rates per 100,000 person-years were consistently higher in patients with asthma than in the referent cohort.

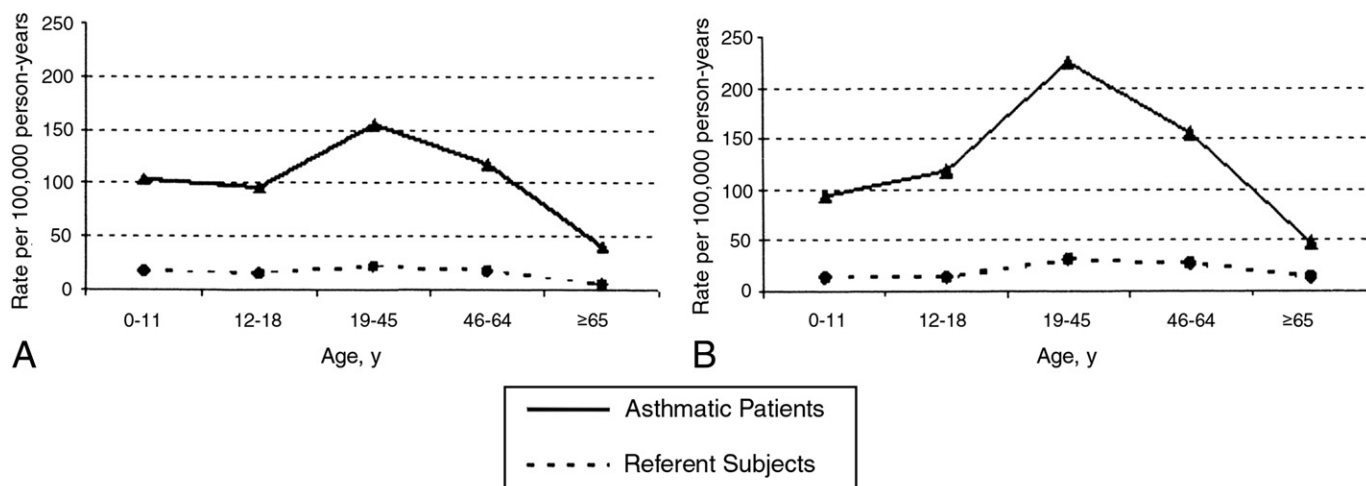


Figure 1. Rates per 100,000 person-years of any anaphylactic shock by age and asthma status in males (A) and females (B).

Table 2. Numbers and Rates per 100,000 Person-years of Anaphylactic Shock and Other Allergy Diagnoses

Outcome	Asthma cohort					Referent cohort				
	Persons, No.	Events, total No.	Rate per 100,000 person-years	No. (%) with >1 event	Events, mean (SD), No.	Persons, No.	Events, total No.	Rate per 100,000 person-years	No. (%) with >1 event	Events, mean (SD), No.
Anaphylactic shock										
Caused by an adverse food reaction	526,021	1,181	40.8	340 (29)	1.5 (1.0)	526,021	248	7.6	58 (23)	1.3 (0.8)
Caused by serum	526,146	1,185	41.0	235 (20)	1.3 (0.6)	526,146	143	4.4	33 (23)	1.4 (0.8)
Other	525,817	1,014	35.1	207 (20)	1.3 (0.8)	525,817	305	9.3	56 (18)	1.3 (1.2)
Any ^a	525,225	3,141	109.0	767 (24)	1.4 (0.9)	525,225	650	19.9	141 (22)	1.3 (0.8)
Other allergy diagnoses										
Allergic urticaria	525,773	1,027	35.5	134 (13)	1.1 (0.4)	525,773	619	18.9	77 (12)	1.1 (0.4)
Anaphylaxis after sting(s)	514,281	9,528	341	1,141 (12)	1.2 (0.5)	514,281	7,757	244	774 (10)	1.1 (0.4)
Angioedema	524,823	3,365	117	938 (28)	1.6 (2.2)	524,823	2,054	62.9	555 (27)	1.5 (1.3)

^a Defined as anaphylactic shock caused by an adverse food reaction or anaphylactic shock caused by serum or other anaphylactic shock.

After adjustment for age, sex, and race/ethnicity, asthma was associated with a 5.4-fold increased risk of any anaphylactic shock (Table 3). The minimally adjusted hazard ratio (HR) ranged, by type of anaphylactic shock, from 3.7-fold higher for other anaphylactic shock to 9.2-fold higher for anaphylactic shock caused by serum and was 5.3-fold higher for anaphylactic shock caused by food. All these HR estimates were minimally affected by further adjustment for prevalent comorbidities and immunotherapy use at baseline (Table 3). Asthma was also significantly associated with subsequent risk of the other 3 selected allergy diagnoses, but the association was weaker than that for anaphylactic shock (HR, 1.4–1.9). Again, the HR estimates for these other allergy diagnoses were minimally altered or unaltered after adjustment for comorbidities and immunotherapy use. Covariates in model 2 significantly associated with the risk of anaphylactic shock were female sex (HR vs male sex, 1.24; 95% confidence interval [CI], 1.16–1.33), age (HR per 5

years, 1.03; 95% CI, 1.02–1.04), Asian race (HR vs whites, 1.41; 95% CI, 1.28–1.56), and previous immunotherapy use (HR vs no use, 5.99; 95% CI, 5.23–6.86).

Table 4 summarizes the results of the analysis of anaphylactic shock in various subgroups. Overall, there was remarkable consistency in the asthma-anaphylactic shock risk relation across the sexes, racial/ethnic groups, and age groups and by immunotherapy use, with no evidence of significant interactions ($P > .11$ for all).

Approximately 4.5% of patients with asthma ($n = 23,723$) met the definition of severe asthma. There was a clear relationship between asthma severity and the risk of anaphylactic shock caused by an adverse food reaction (Table 5). In the fully adjusted model (model 2), nonsevere asthma was associated with a 5.0-fold increased hazard of anaphylaxis due to food, whereas severe asthma was associated with an 8.2-fold increased hazard of food-related anaphylactic shock. There was also evidence of effect modification by asthma severity

Table 3. Results of Cox Proportional Hazards Regression Assessing Risk of Anaphylactic Shock and Other Allergy Diagnoses Associated With Asthma

Outcome	Hazard ratio (95% confidence interval) ^a	
	Model 1 ^b	Model 2 ^c
Anaphylactic shock		
Caused by an adverse food reaction	5.29 (4.61–6.07)	5.26 (4.58–6.03)
Caused by serum	9.23 (7.76–10.98)	8.18 (6.87–9.74)
Other	3.74 (3.29–4.25)	3.69 (3.24–4.19)
Any	5.42 (4.98–5.9)	5.17 (4.75–5.63)
Other allergy diagnoses		
Allergic urticaria	1.90 (1.72–2.10)	1.88 (1.70–2.07)
Anaphylaxis after sting(s)	1.37 (1.33–1.41)	1.37 (1.33–1.41)
Angioedema	1.88 (1.78–1.98)	1.86 (1.76–1.97)

^a $P < .001$ for all.

^b Model 1 includes age, sex, and race/ethnicity.

^c Model 2 further adjusts for prevalent comorbidities and history of immunotherapy use.

of the hazard of other (idiopathic) anaphylactic shock, but the magnification of the hazard as a result of severe asthma was not as marked as that seen for food-related anaphylactic shock. In contrast, there was no significant effect of severity of asthma on anaphylactic shock due to serum. Severe asthma was also associated with a greater hazard of anaphylaxis after sting(s). No significant effect of severity of asthma was apparent for allergic urticaria, and a paradoxical lessening of the hazard with severity of asthma was seen for angioedema.

DISCUSSION

Previous studies have shown associations between asthma or history of atopic disease and anaphylactic reactions. However, these studies^{3,14–17} provided limited quantifiable evidence regarding this association because they were based on case reports that lacked a comparison group. In this study of a large managed care population, we found that asthmatic patients (compared with individuals with no history of asthma) had a 5.2-fold increased incidence of any type of anaphylactic shock, irrespective of age, sex, race/ethnicity, several selected comorbidities, and immunotherapy use. This association was particularly striking for anaphylactic shock due to serum, and followed, in strength, by anaphylactic reaction due to food and by other/idiopathic anaphylactic shock. Asthma was also associated with enhanced risk of other selected allergy diagnoses, ie, allergic urticaria, anaphylaxis after sting(s), and angioedema. The asthma–anaphylactic shock risk relation was remarkably uniform across sex, race/ethnicity, and age subgroups. Finally, we found clear effects of asthma severity in the case of anaphylactic shock due to food, other/idiopathic anaphylactic shock, and anaphylaxis after sting(s).

Anaphylactic shock is a potentially life-threatening condition. However, its epidemiologic features have not been well defined and quantified, which limits identification of patients at greatest risk. Accordingly, a systematic review conducted by the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group concluded that population-based studies of anaphylaxis are needed to better define the incidence and risk factors for anaphylaxis.¹⁸

Table 4. Results of Cox Proportional Hazards Regression Assessing Risk of Any Anaphylactic Shock Associated With Asthma According to Sex, Race/Ethnicity, Age, and Immunotherapy Use

Strata	Patients/events, No.	Hazard ratio (95% confidence interval) ^a	
		Model 1 ^b	Model 2 ^c
Sex			
Men	481,598/1,458	5.21 (4.55–5.96)	4.99 (4.36–5.71)
Women	568,852/2,333	5.55 (4.98–6.19)	5.28 (4.73–5.89)
Race/ethnicity			
Asian	100,362/549	4.54 (3.67–5.62)	4.30 (3.47–5.33)
Black	77,414/284	4.20 (3.14–5.61)	4.12 (3.08–5.51)
Latino/Hispanic	93,854/360	5.49 (4.16–7.24)	5.11 (3.86–6.76)
Mixed	43,588/197	5.97 (4.05–8.81)	6.00 (4.06–8.85)
American Indian	5,956/22	10.8 (2.51–46.1)	9.08 (2.1–39.24)
White	397,418/1,722	5.34 (4.71–6.05)	5.07 (4.47–5.75)
Unknown/other	331,858/657	7.06 (5.68–8.78)	6.73 (5.41–8.37)
Age			
0–11	396,268/1,018	4.70 (4.01–5.5)	4.59 (3.92–5.38)
12–18	124,872/333	4.87 (3.69–6.41)	4.69 (3.55–6.19)
19–45	346,152/1,658	5.99 (5.25–6.83)	5.70 (5.00–6.50)
46–64	130,798/690	5.95 (4.83–7.32)	5.47 (4.44–6.74)
≥65	52,360/92	4.02 (2.45–6.6)	3.64 (2.21–6.02)

^a $P < .001$ for all.

^b Model 1 includes age, sex, and race/ethnicity.

^c Model 2 further adjusts for prevalent comorbidities and history of immunotherapy use.

Table 5. Results of Cox Proportional Hazards Regression Assessing Risk of Anaphylactic Shock and Other Allergy Diagnoses Associated With Asthma Severity

Outcome	Nonsevere asthma		Severe asthma	
	Patients/events, No.	Model 2 hazard ratio (95% CI) ^a	Subjects/events, No.	Model 2 hazard ratio (95% CI) ^a
Anaphylactic shock				
Caused by an adverse food reaction	502,308/1,054	5.05 (4.39–5.80)	23,713/127	8.23 (6.59–10.27)
Caused by serum	502,425/1,097	8.32 (6.98–9.92)	23,721/88	6.55 (4.99–8.61)
Other	502,162/889	3.56 (3.12–4.05)	23,655/125	5.06 (4.07–6.28)
Any	501,580/2,832	5.09 (4.67–5.55)	23,645/309	6.08 (5.29–7)
Other allergy diagnoses				
Allergic urticaria	502,101/953	1.90 (1.72–2.11)	23,672/74	1.58 (1.23–2.02)
Anaphylaxis after sting(s)	490,851/8,714	1.35 (1.31–1.39)	23,430/814	1.64 (1.53–1.77)
Angioedema	501,162/3,060	1.89 (1.78–2.00)	23,661/305	1.64 (1.45–1.85)

Abbreviation: CI, confidence interval.

^a Relative to control subjects (n=526,406). *P*<.001 for all.

The present study, which reports the incidence and factors associated with anaphylaxis in a large population, addresses this need. We found that the incidence of any anaphylactic shock in asthma-free subjects (20 per 100,000 person-years) was somewhat lower than that estimated in residents of Olmsted County, Minnesota (age range, 6 months to 89 years; mean age, 29 years), from 1983 through 1987 (30 per 100,000 person-years).⁶ This discrepancy may be related to several factors, including differences in (1) study design (cohort vs case-control), (2) the fact that the Minnesota population may have contained patients with asthma, (3) methods of ascertainment of anaphylactic shock, or (4) the demographic characteristics of each population (Olmsted County residents are 95% white, and a high proportion is employed in the health care industry). Bohlke et al³ reported an incidence of 10.5 per 100,000 person-years in children and adolescents enrolled in Group Health Cooperative in western Washington state. This lower figure, compared with that in the present study, may reflect differences in age and in methods (the Group Health Cooperative study confirmed each case regardless of diagnosis).

The strengths of the present study include the very large samples of asthmatic patients and referent subjects, the availability of a validated algorithm to define asthma severity,¹³ longitudinal follow-up through automated health plan databases, the ethnic diversity of the sample, the satisfactory validation of other (idiopathic) anaphylactic shock using medical record review, and the fact that the data reflect a real-world health care setting. Several limitations should be pointed out. First, the observational nature of the data precludes causal inference. Second, because wheeze bronchospasm is a criterion for anaphylactic shock, the strength of the asthma–anaphylactic shock association found herein may have been inflated by attribution bias (the possibility that patients with asthma may have been more likely to receive a diagnosis of anaphylactic shock compared with patients without asthma). Third, we did not validate anaphylactic shock due to food or serum and the selected allergy diagnoses.

Fourth, we did not have data on biomarkers of anaphylaxis (ie, mast cell–derived mediators such as histamine or tryptase) that may have provided confirmatory evidence of an anaphylactic reaction. Fifth, we did not examine anaphylactic reactions to specific drug exposures (ie, penicillin) or to anesthesia because this was beyond the scope of this study, and, last, we did not have objective clinical measures, such as spirometry, total serum or specific IgE levels, or skin allergy testing, and, therefore, were unable to differentiate asthma into different phenotypes, namely, IgE mediated, allergic but not IgE mediated, or nonallergic asthma. Whether the prospective association between asthma and anaphylactic reactions differ by asthma phenotype is, therefore, a topic for further research.

Children and adults with asthma across a wide range of ages and ethnic backgrounds are susceptible to an increased risk of anaphylactic shock, particularly anaphylactic shock due to serum and food. Health professionals should be aware of this connection and should have an increased level of suspicion for anaphylactic shock in asthmatic patients with respiratory, cutaneous, or cardiovascular complaints. Clinical trials of asthma therapies that may induce allergic reactions should also take into account the potential increased risk of anaphylaxis in persons with asthma.

ACKNOWLEDGMENT

The sponsor did not have access to individual-level data but had an opportunity to review and comment on the final draft of the manuscript. The authors affiliated with Kaiser Permanente Division of Research (Dr Iribarren and Ms Tolstykh) had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

SUPPLEMENTARY DATA

Additional tables accompany the on-line version of the article (available at <http://www.annallergy.org>).

REFERENCES

1. Braman SS. The global burden of asthma. *Chest*. 2006;130(suppl): 4S–12S.
2. Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma--United States, 1980–1999. *MMWR Surveill Summ*. 2002;51:1–13.
3. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol*. 2004;113:536–542.
4. Matasar MJ, Neugut AI. Epidemiology of anaphylaxis in the United States. *Curr Allergy Asthma Rep*. 2003;3:30–35.
5. Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med*. 2004;164:317–319.
6. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol*. 1999;104:452–456.
7. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. *Am J Public Health*. 1992;82:703–710.
8. Eisner MD, Ackerson LM, Chi F, et al. Health-related quality of life and future health care utilization for asthma. *Ann Allergy Asthma Immunol*. 2002;89:46–55.
9. Eisner MD, Lieu TA, Chi F, et al. β -Agonists, inhaled steroids, and the risk of intensive care unit admission for asthma. *Eur Respir J*. 2001;17: 233–240.
10. Lieu TA, Capra AM, Quesenberry CP, Mendoza GR, Mazar M. Computer-based models to identify high-risk adults with asthma: is the glass half empty or half full? *J Asthma*. 1999;36:359–370.
11. Erickson S, Tolstykh I, Selby JV, Mendoza G, Iribarren C, Eisner MD. The impact of allergy and pulmonary specialist care on emergency asthma utilization in a large managed care organization. *Health Serv Res*. 2005;40:1443–1465.
12. 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. *J Allergy Clin Immunol*. 2006;117:391–397.
13. Eisner MD, Boland M, Tolstykh I, Mendoza G, Iribarren C. Intensive care unit admission for asthma: a marker for severe disease. *J Asthma*. 2005;42:315–323.
14. Banov C. Current review of anaphylaxis and its relationship to asthma. *Allerg Immunol (Paris)*. 1991;23:417–420.
15. Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol*. 2001;107:191–193.
16. Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol*. 2001; 108:861–866.
17. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992;327: 380–384.
18. 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.

Requests for reprints should be sent to:
Carlos Iribarren, MD, PhD, MPH
Division of Research
Kaiser Permanente Medical Care Program
2000 Broadway
Oakland, CA 94612
E-mail: cgi@dor.kaiser.org

Supplementary Table 1. Number and Rates per 100,000 Person-Years of Anaphylactic Shock and Other Allergy Diagnoses

Outcome	Asthma Cohort					Referent Cohort				
	Persons, No.	Events, No.	Rate per 100,000 person-years	No. (%) with >1 event	No. of events, mean (SD)	Persons, No.	Events, No.	Rate per 100,000 person-years	No. (%) with >1 event	No. of events, mean (SD)
Anaphylactic shock										
Caused by an adverse food reaction	365,249	1,075	50.4	326 (30)	1.5 (1.1)	365,249	174	7.3	42 (24)	1.3 (0.8)
Caused by serum	365,326	1,096	51.4	221 (20)	1.3 (0.6)	365,326	113	4.8	27 (24)	1.4 (0.7)
Other	365,073	896	42.1	180 (20)	1.3 (0.8)	365,073	233	9.8	46 (20)	1.3 (0.8)
Any ^a	364,625	2,850	134.4	715 (25)	1.4 (0.9)	364,625	484	20.4	110 (23)	1.4 (0.8)
Other allergy diagnoses										
Allergic urticaria	365,048	826	38.7	104 (13)	1.1 (0.4)	365,048	452	19.0	55 (12)	1.1 (0.4)
Anaphylaxis after sting(s)	356,691	7,409	360.8	940 (13)	1.2 (0.6)	356,691	5,829	253.8	617 (11)	1.1 (0.5)
Angioedema	364,298	2,920	137.6	823 (28)	1.6 (2.4)	364,298	1,600	67.6	450 (28)	1.6 (1.3)

^a Defined as anaphylactic shock caused by an adverse food reaction or anaphylactic shock caused by serum or other anaphylactic shock.

Supplementary Table 2. Results of Cox Proportional Hazards Regression Assessing Risk of Anaphylactic Shock and Other Allergy Diagnoses Associated With Asthma

Outcome	Hazard ratio (95% confidence interval) ^a	
	Model 1 ^b	Model 2 ^c
Anaphylactic shock		
Caused by an adverse food reaction	6.80 (5.79–7.99)	6.75 (5.75–7.93)
Caused by serum	10.66 (8.78–12.94)	9.46 (7.78–11.49)
Other	4.27 (3.69–4.94)	4.21 (3.64–4.87)
Any	6.53 (5.93–7.20)	6.23 (5.65–6.86)
Other allergy diagnoses		
Allergic urticaria	2.07 (1.84–2.32)	2.04 (1.81–2.29)
Anaphylaxis after sting(s)	1.40 (1.35–1.45)	1.40 (1.35–1.44)
Angioedema	2.07 (1.95–2.20)	2.05 (1.93–2.19)

^a $P < .001$ for all.

^b Model 1 includes age, sex, and race/ethnicity.

^c Model 2 further adjusts for prevalent comorbidities and history of immunotherapy use.