

Anaphylaxis epidemiology in patients with and without asthma: A United Kingdom database review

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Background: There are currently limited data regarding the epidemiology of anaphylaxis.

Objective: To estimate the incidence of anaphylaxis from all causes, to explore the variety of diagnoses that may predispose to an anaphylactic episode, and to estimate the rate of recurrence of anaphylaxis in patients with no asthma, nonsevere asthma, and severe asthma.

Methods: The Health Improvement Network database provided data on individuals 10 to 79 years old who had been enrolled for at least 1 year with a general practitioner in the United Kingdom and had at least 1 health contact in the year before entering the study.

Results: Anaphylaxis incidence rates (per 100,000 person-years) were 21.28 (95% CI, 17.64-25.44) and 50.45 (95% CI, 44.67-56.76) in the no asthma and overall asthma cohorts, respectively. Risk of anaphylaxis was greater in the nonsevere asthma (relative risk, 2.07; 95% CI, 1.65-2.60) and severe asthma (relative risk, 3.29; 95% CI, 2.47-3.47) subgroups compared with the no asthma cohort. The incidence rate of anaphylaxis was higher in women than men (22.65 vs 19.56 per 100,000 person-years). Within the overall asthma population, patients at significantly increased risk of anaphylaxis included those with allergic rhinitis or atopic dermatitis, and current users of antihistamines, oral steroids, or antibiotics (compared with nonusers). Drug and food allergies were the most common known causes of anaphylaxis.

Conclusion: Patients with asthma have a greater risk of anaphylaxis than those without asthma, and the risk is greater in severe than nonsevere asthma. Women are at higher risk of anaphylaxis than men, especially those with severe asthma. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: Asthma, anaphylaxis, epidemiology

Abbreviations used

GP: General practitioner
ICD: International Classification of Diseases
NSAID: Nonsteroidal anti-inflammatory drug
OR: Odds ratio
RR: Relative risk
THIN: The Health Improvement Network
UK: United Kingdom

The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network have recommended that anaphylaxis be defined as “a serious allergic reaction that is rapid in onset and may cause death” and is likely to be the diagnosis when there is involvement of skin or mucosal tissue (eg, hives, angioedema) and airway compromise (wheezing, dyspnea) and/or reduced blood pressure or associated symptoms (hypotonia, syncope), along with a temporal relationship (minutes to several hours) to a potential causative agent.¹ Anaphylactic reactions can be triggered by allergic responses to a wide range of substances, including food, medications, wasp or bee stings, and latex.²

Key challenges to the study of anaphylaxis are a lack of widely accepted standard working definitions,³⁻⁶ inadequate reporting of events, failure to agree on a severity threshold for classification as an anaphylactic reaction, and unfamiliarity with the variable presentation. Consequently, few studies of anaphylaxis epidemiology have been completed.

We sought to estimate the incidence of anaphylaxis from all causes, explore predisposing diagnoses, estimate the rate of anaphylaxis recurrence, and analyze the association between anaphylaxis and asthma.

METHODS

Data sources

The Health Improvement Network (THIN) database contains data from more than 2.3 million patients registered with over 300 general practices. Most contributing practices had several years of data, with some entries extending back to 1985.

The Health Improvement Network data are collected in a noninterventive manner based on daily record keeping in general practice. THIN data are processed by the EPIC Database Research Company Ltd, London, United Kingdom (UK), to provide researchers with full, coded demographic, medical and prescription details at the individual patient level.⁷

Cohort definition

The study population was derived from individuals (age 10-79 years) enrolled for at least 1 year with a general practitioner (GP) and with at least

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1 health contact in the year before entering the study. The study period was from January 1, 1996, to December 31, 2005. The study population was divided into 3 groups. The asthma cohort included all patients with a diagnosis of asthma corresponding to International Classification of Diseases (ICD)–9 codes 493.0 (“extrinsic asthma”), 493.1 (“intrinsic asthma”), and 493.9 (“asthma unspecified”) during or before the study period. Severe asthma was defined similarly to previously published criteria⁸ and included patients with at least 1 of the following: (1) asthma hospitalization, (2) ≥ 3 prescriptions for oral corticosteroids within 1 year, (3) ≥ 12 prescriptions for inhaled β_2 -agonists within 1 year, or (4) ≥ 3 classes of asthma medications within 1 year. Patients with asthma who did not meet severe asthma criteria were included in the non-severe asthma subgroup.

The no asthma cohort in this study was a random sample of 200,000 individuals without a diagnosis of asthma, frequency-matched to the asthma cohort by age, sex, and cohort start date.

Follow-up started from the date when an individual met all eligibility criteria and ended at the earliest date of (1) diagnosis of anaphylaxis, (2) death, (3) end of the study period, or (4) end of follow-up in the database.

Identification of cases

A 2-tiered approach was used to identify cases. Automated files were searched for all entries corresponding to the ICD-9 codes 995.0 (“other anaphylactic shock”), 995.4 (“shock caused by anesthesia”), and 995.6 (“anaphylactic shock due to adverse food reaction”).

The occurrence of less specific terms was also determined to estimate the frequency of anaphylaxis among these other diagnoses: 693.1 (“dermatitis due to food”), 695.1 (“erythema multiforme”), 708.0 (“allergic urticaria”), 708.9 (“urticaria unspecified”), 989.5 (“toxic effect of venom”), 995.1 (“angio-neurotic edema”), and 995.3 (“allergy, unspecified”). Some cases of anaphylaxis may be recorded under these diagnoses.^{9–11}

Potential cases of anaphylaxis were validated by contacting GPs who completed a questionnaire (see this article’s Fig E1 in the Online Repository at www.jacionline.org) by using original medical records and/or any hospital or specialists’ reports. A recurrent case was defined as an incident case that experienced a second episode. GPs either confirmed or discarded suspected incident cases and provided additional details such as date of onset, likely cause, accompanying symptoms, and date of recurrence (where appropriate).

Analysis

Anaphylaxis incidence was estimated on the basis of validated incident cases. Person-time was calculated for each member of the cohort as the time contributed to the study period. Population-based incidence estimates of anaphylaxis were then tabulated for each group. Age-specific and sex-specific anaphylaxis incidence rates were estimated. Where patients changed age stratum during the study period, person-time within each age group was allocated accordingly.

Incidence rate estimations were calculated as the number of cases divided by the person-time at risk. Poisson distribution was used to generate 95% CIs. Crude anaphylaxis recurrence rates were calculated in all patients with a first anaphylactic event by following up until there was a second anaphylactic event (third episodes were not considered), the study period ended, or the individual died. Person-time from the first episode onwards was considered for this calculation. Poisson regression was used to calculate rate ratio with adjustments for age, sex, calendar year (to investigate specific influences in any calendar year), and body mass index. Time at risk was used as an offset variable. Risk factors for anaphylaxis (other medical conditions and previous/current medication use) were investigated in a nested case-control study. For this analysis, all validated incident cases in the no asthma or asthma cohorts were used. Five thousand controls from each cohort were randomly selected from the list of eligible controls and frequency-matched to the cases on sex, age, and calendar year. In the analyses of drug use, the reference date was (1) the date that anaphylaxis was diagnosed in cases or (2) the index date in controls. Risk of anaphylaxis was statistically significant if the 95% CI for the odds ratio (OR) did not encompass the value 1.0.

In addition, a sensitivity analysis was performed in which only those cases with a specific diagnosis of anaphylactic shock requiring hospital admission were examined.

RESULTS

Study populations

The asthma population included 177,000 patients with a diagnosis of asthma: 131,872 patients (74.5%) had nonsevere asthma and 45,103 patients (25.5%) had severe asthma (identified by ≥ 12 prescriptions for inhaled β_2 -agonists within 1 year [20,030 patients (11.3%)]; ≥ 3 classes of asthma medications within 1 year [11,618 patients (6.6%)]; ≥ 3 prescriptions for oral corticosteroids within 1 year [11,336 patients (6.4%)]; and asthma hospitalization [2119 patients (1.2%)]).

Medical record validation

After applying exclusion criteria, 675 cases of anaphylaxis were identified, and of the 619 returned questionnaires, 609 contained valid information (98%) and 444 (72%) cases were confirmed. Sixty-two of the confirmed cases did not occur within the study period; therefore, 382 confirmed cases (62% of returned questionnaires) were considered valid incident cases. Cases with specific diagnostic codes had a higher confirmation rate (85.3%) than cases with a nonspecific diagnostic code (70.2%).

Incidence of anaphylaxis

Of the 382 confirmed incident cases of anaphylaxis, 262 occurred in the asthma cohort and 120 in the no asthma cohort.

The calculated anaphylaxis incidence rate was 21.28 per 100,000 person-years (95% CI, 17.64–25.44) in the no asthma cohort and 50.45 per 100,000 person-years (95% CI, 44.67–56.76) in the asthma cohort. The incidence rate of anaphylaxis was 43.01 cases per 100,000 person-years (95% CI, 37.02–49.70) in individuals with nonsevere asthma and 65.35 cases per 100,000 person-years (95% CI, 51.66–81.56) in individuals with severe asthma (Table I). The incidence of anaphylaxis was higher in women in both cohorts, particularly in the asthma population (90.6% and 69.1% higher incidence in females in the severe and nonsevere cohorts, respectively, compared with 15.8% in the no asthma cohort). The incidence of anaphylaxis across different age groups and sexes is shown in Fig 1. In the asthma cohort, relative differences between sexes were more pronounced in the age groups 20 to 49 years. We also show the incidence rates of anaphylactic shock (as defined in the sensitivity analysis) in the study cohorts. A total of 55 cases met these criteria. The corresponding rates in the 3 cohorts (no asthma, nonsevere asthma, and severe asthma) were 2.48 (95% CI, 1.36–4.16), 5.61 (95% CI, 3.59–8.35), and 14.24 (95% CI, 8.30–22.80) cases per 100,000 person-years, respectively (Table I).

Of the 382 validated cases of anaphylaxis, 82 patients had more than 1 anaphylactic reaction. The incidence rates of recurrent anaphylaxis were 10.7, 8.2, and 5.5 per 100 person-years in the no asthma cohort, the nonsevere asthma subgroup, and the severe asthma subgroup, respectively. The difference between the no asthma and asthma cohorts was not significant ($P = .11$), but that between the no asthma cohort and the severe asthma subgroup was just significant ($P = .05$).

TABLE I. Incidence rates for anaphylaxis and anaphylactic shock (cases per 100,000 person-years)

	Person-years	Anaphylaxis		Anaphylactic shock	
		Cases	IR	Cases	IR
Total population	1,111,124.0	382	34.38	55	4.95
No asthma cohort	563,997.8	120	21.28	14	2.48
Male	250,551.4	49	19.56	6	2.39
Female	313,446.4	71	22.65	8	2.55
Nonsevere asthma	427,770.7	184	43.01	24	5.61
Male	189,900.1	59	31.07	8	4.21
Female	237,870.6	125	52.55	16	6.73
Severe asthma	119,355.1	78	65.35	17	14.24
Male	52,941.3	23	43.44	4	7.56
Female	66,413.8	55	82.81	13	19.57

IR, Incidence rate.

Risk factors for anaphylaxis

The risk of anaphylaxis was 2-fold greater (relative risk [RR], 2.07; 95% CI, 1.65-2.60) in the nonsevere asthma subgroup and 3-fold greater (RR, 3.29; 95% CI, 2.47-3.47) in the severe asthma subgroup compared with the no asthma cohort in the Poisson analyses. The corresponding RRs for the subgroup of anaphylactic shock cases as defined in the sensitivity analysis were 2.26 (95% CI, 1.12-4.73) and 5.74 (95% CI, 2.67-12.57).

In the case-control study, atopic dermatitis was the only factor associated with a significantly increased risk of anaphylaxis within the no asthma cohort (OR, 2.83; 95% CI, 1.51-5.29; Table II). Within the asthma cohort, patients with allergic rhinitis (OR, 1.76; 95% CI, 1.35-2.30), atopic dermatitis (OR, 1.69; 95% CI, 1.13-2.51) and osteoarthritis (OR, 1.50; 95% CI, 1.05-2.14) were at significantly increased risk of anaphylaxis.

Analysis of drug use (compared with nonusers) found that in the no asthma cohort, current and previous users of antibiotics and previous users of lipid-lowering drugs were at a significantly increased risk of anaphylaxis (Table III). In the asthma cohort, current users of antihistamines, oral corticosteroids, or antibiotics were at a significantly higher risk of anaphylaxis (Table IV), as were previous users of H₂-blockers and other medications highlighted in Table IV. Notably, current users of antimuscarinic medication were at a significantly lower risk of anaphylaxis.

In the sensitivity analysis, only validated cases with a specific diagnosis of anaphylactic shock that required emergency admission to a hospital were considered in the multivariate logistic regression models. Despite the limited power because of small patient numbers, we were able to observe similar results to those obtained with the overall population. Thus, in this analysis, severe asthma was associated with an OR of 2.86 (0.85-9.60), whereas nonsevere asthma was associated with an OR of 1.26 (0.48-3.34); the corresponding ORs from the main analysis were 2.81 (1.78-4.43) and 1.40 (1.01-1.93) for severe and nonsevere asthma, respectively, compared with those free of asthma. Other main risk factors of anaphylaxis in our study such as atopic dermatitis and antibiotic use were also consistent in both analyses (ie, anaphylactic shock cases only and all cases of anaphylaxis). Thus, the estimates of atopic dermatitis were 1.95 (0.75-5.08) and 7.76 (1.98-30.37) in the asthma and no asthma cohorts, respectively, compared with 1.69 (1.13-2.51) and 2.83 (1.51-5.29) from the main analysis (Table II). Similarly, the estimates of antibiotic use were 1.46 (0.57-3.75) and 13.19 (3.44-50.59) in the asthma and no asthma cohorts, respectively, compared with 1.61 (1.08-2.39) and 5.62 (3.32-9.53) from the main analysis

(Tables III and IV). All these estimates are remarkably consistent considering the small number of cases in these analyses (3 and 5 cases of anaphylactic shock with atopic dermatitis in the no asthma and asthma populations, respectively).

Anaphylaxis causes, signs and symptoms, and health care use

Drug allergy was the most common known cause of anaphylaxis (n = 102; 27% of cases; Table V) and was predominantly associated with antibiotics (n = 39), nonsteroidal anti-inflammatory drugs (NSAIDs; n = 8), and antihypertensive medications (n = 5). Amoxicillin was the most prevalent cause of antibiotic-related anaphylaxis (n=13). The incidence of drug-related anaphylaxis was highest in those with severe asthma. Food was the second most common cause of anaphylaxis (24%) followed by insect stings (12%). Food-related anaphylaxis was highest in those with nonsevere asthma. Among young individuals (less than 40 years of age), food-related anaphylaxis was also the most common cause of anaphylaxis, accounting for 60 of 175 observed cases (35%), followed by drug-related anaphylaxis (15%). The rate of anaphylaxis of unknown cause was highest in the no asthma cohort.

The most common manifestation of anaphylaxis was mucocutaneous signs and symptoms (75% of cases), followed by respiratory signs and symptoms (31%). Respiratory signs and symptoms were more common in the asthma cohorts (severe, 46%; nonsevere, 36%) than the no asthma cohort (15%).

Forty-nine percent of anaphylactic episodes were encountered in a hospital setting, and 15% were observed during an outpatient or primary care visit for which there was no need for further referral. The remainder were reported after the event—for example, during a subsequent GP visit—and medical assistance was not required. None of the anaphylaxis cases had a fatal outcome.

DISCUSSION

Our study is the first to evaluate the frequency of anaphylaxis in patients with severe or nonsevere asthma. We found the anaphylaxis incidence rate in individuals with asthma to be substantially higher than that in patients without asthma (50.45 vs 21.28 per 100,000 person-years). Also, patients with severe asthma were more likely to experience anaphylaxis than those with nonsevere asthma (65.35 vs 43.01 cases per 100,000 person-years).

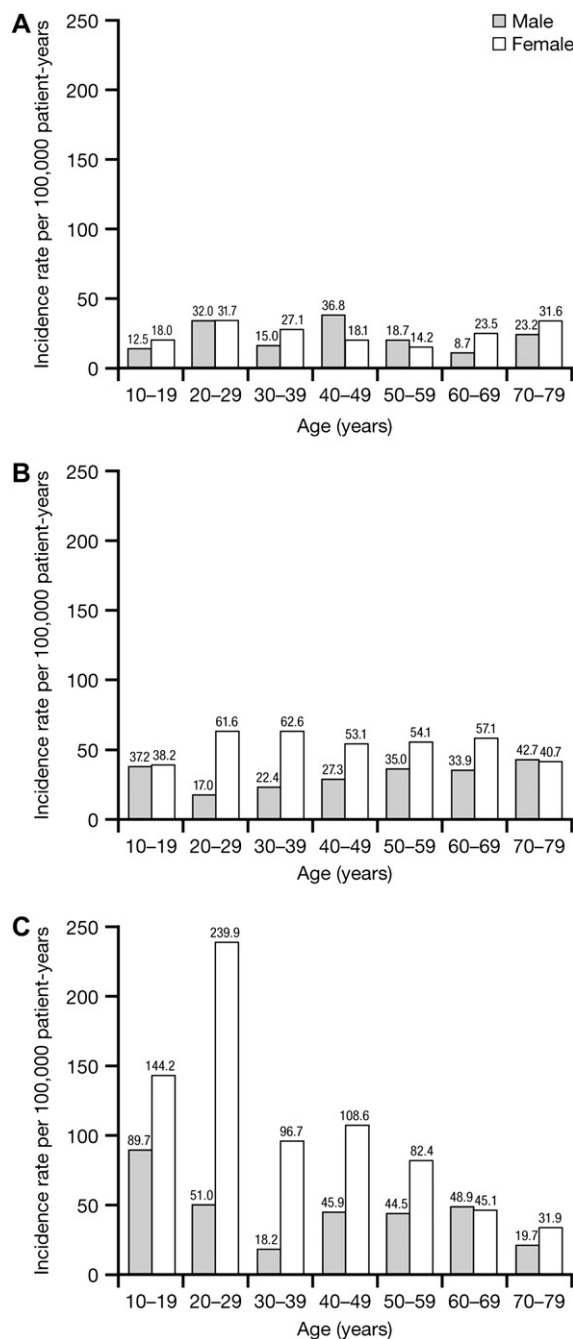


FIG 1. Incidence rate of anaphylaxis (cases per 100,000 person-years) by age and sex in the no asthma cohort (A), the nonsevere asthma subgroup (B), and the severe asthma subgroup (C).

Furthermore, there was a 3.3-fold greater risk of anaphylaxis in individuals with severe asthma and a 2-fold greater risk in those with nonsevere asthma compared with patients without asthma.

The incidence of anaphylaxis in the no asthma cohort reported here approximates that estimated in the literature. The most meaningful comparisons with our findings are those provided by other UK-based assessments of anaphylaxis incidence in the general population. An observational follow-up study based on the UK General Practice Research Database (1994-1999) reported an anaphylaxis incidence rate of 8.4 cases per 100,000 person-years.¹² A recent analysis of UK data from the QRESEARCH

database found that the age-standardized and sex-standardized incidence of anaphylaxis increased from 6.7 to 7.9 per 100,000 person-years during the period 2001 to 2005.¹³ A US study of pediatric and adolescent records in a large health maintenance organization database estimated the incidence of anaphylaxis to be 10.5 episodes per 100,000 person-years, with no increase over time.⁹ However, subsequent inclusion of both specific and nonspecific codes for anaphylaxis in their analysis increased the incidence rate to 68.4 episodes per 100,000 person-years.

Another US study that retrospectively identified cases of anaphylaxis ICD codes (1990-2000) found an overall age-adjusted and sex-adjusted incidence rate of 49.8 per 100,000 person-years.¹⁴ Recognizing the diversity of study designs and criteria, and sparse and often imprecise data, a roundtable review of hand-picked literature dating back to 1968 from various countries led to an estimation of the frequency of anaphylaxis of between 50 and 2000 episodes per 100,000 persons, or a lifetime prevalence of 0.05% to 2.0%.¹⁵ A Canadian study of epinephrine dispensing patterns found that 0.95% of the general population had epinephrine dispensed for out of hospital treatment, with the highest rate in patients <17 years (1.44%), followed by those age ≥17 to <65 years (0.9%) and ≥65 years (0.32%).¹⁶ Although research gives an indication of the level of anaphylaxis in the general population, variability in the results makes it difficult to provide definitive conclusions on the overall incidence of anaphylaxis and highlights the need for standardized working definitions to be generated.

Our study found a higher incidence of anaphylaxis in women than in men, particularly among individuals with severe asthma, although it has been reported that the risk of anaphylaxis is higher in boys.^{9,14,16} No deaths occurred in our study, and this observation is consistent with the low incidence of fatal anaphylaxis seen in previous studies.^{12,17}

Our findings that medications and food are the most frequent causes of anaphylaxis and that no specific cause can be identified in a substantial proportion of patients are consistent with reports from other studies.^{14,18} We highlighted NSAID use as potential cause of anaphylaxis; although not significantly associated with anaphylaxis in either cohort, 8 of the 382 validated cases indicated NSAIDs as a possible cause. That we did not detect an association between NSAIDs and anaphylaxis is probably a result of their widespread use. Food (22%), medication (11%), and exercise (5%) have been reported as causes of anaphylaxis.¹⁹ Anaphylaxis of unknown cause has been reported in 37% to 59% of cases.^{5,19} A French survey of 33,000 people found that 3.2% of individuals had a food allergy.²⁰ Food-induced anaphylaxis was the second most common cause in our study, but food allergies have been reported elsewhere as the most common cause of anaphylaxis.²¹

Although some individuals who are aware of their own specific anaphylactic triggers will attempt to avoid them, it is not always known who may be susceptible. The most frequent manifestations of anaphylaxis in our study were cutaneous signs and symptoms in both the no asthma (80%) and asthma (73%) cohorts. Unfortunately, we could not obtain information regarding symptoms in approximately 14% of our study population. If we consider only patients with full information, the proportions of cases with skin findings increase to 92% and 84% respectively. Respiratory symptoms were the next most frequent manifestation of anaphylaxis, occurring in 46% of the severe asthma subgroup, 36% of the nonsevere asthma subgroup, and 5% of the no asthma cohort.

TABLE II. Medical conditions and the risk of anaphylaxis in the no asthma and asthma cohorts

Risk factor	No asthma cohort			Asthma cohort		
	Controls (n = 5000) n (%)	Cases (n = 120) n (%)	OR* (95% CI)	Controls (n = 5000) n (%)	Cases (n = 262) n (%)	OR* (95% CI)
Allergic rhinitis	426 (8.5)	17 (14.2)	1.61 (0.95-2.75)	1203 (24.1)	94 (35.9)	1.76 (1.35-2.30)
Atopic dermatitis	178 (3.6)	12 (10.0)	2.83 (1.51-5.29)	354 (7.1)	31 (11.8)	1.69 (1.13-2.51)
COPD	21 (0.4)	0 (0)	—	515 (10.3)	24 (9.2)	0.85 (0.53-1.35)
Diabetes	199 (4.0)	3 (2.5)	0.56 (0.17-1.83)	206 (4.1)	16 (6.1)	1.48 (0.84-2.58)
Hypertension	793 (15.9)	19 (15.8)	0.92 (0.53-1.61)	904 (18.1)	51 (19.5)	1.07 (0.75-1.54)
IBD	43 (0.9)	2 (1.7)	1.68 (0.40-7.15)	46 (0.9)	4 (1.5)	1.55 (0.55-4.43)
IBS	212 (4.2)	8 (6.7)	1.44 (0.68-3.04)	380 (7.6)	19 (7.3)	0.84 (0.51-1.37)
IHD	259 (5.2)	7 (5.8)	1.12 (0.49-2.57)	305 (6.1)	17 (6.5)	0.99 (0.57-1.71)
Immunizations	3767 (75.3)	93 (77.5)	1.06 (0.67-1.66)	4303 (86.1)	231 (88.2)	1.13 (0.76-1.67)
Rheumatoid arthritis	51 (1.0)	1 (0.8)	0.70 (0.09-5.20)	85 (1.7)	8 (3.1)	1.59 (0.74-3.40)
Osteoarthritis	622 (12.4)	21 (17.5)	1.48 (0.86-2.56)	805 (16.1)	57 (21.8)	1.50 (1.05-2.14)
Psoriasis	133 (2.7)	6 (5.0)	1.7 (0.72-4.00)	153 (0.03)	14 (0.05)	1.56 (0.88-2.78)

COPD, Chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; IBS, inflammatory bowel syndrome; IHD, ischemic heart disease.

Statistically significant ORs are in boldface.

*Estimates adjusted by age, sex, calendar year, body mass index, and all variables in the table using an unconditional logistic regression model.

TABLE III. Drug use and risk of anaphylaxis in the no asthma cohort

Drug	Use status*	Controls (n = 5000) n (%)	Cases (n = 120) n (%)	OR† (95% CI)
Antibiotics	Current	273 (5.5)	26 (21.7)	5.62 (3.32-9.53)
	Past	1190 (23.8)	41 (34.2)	2.09 (1.35-3.23)
Antidepressants	Current	303 (6.1)	12 (10.0)	1.34 (0.68-2.62)
	Past	177 (3.5)	2 (1.7)	0.35 (0.08-1.47)
Antidiabetics	Current	141 (2.8)	1 (0.8)	0.29 (0.07-1.67)
	Past	15 (0.3)	0	—
Antihypertensives	Current	737 (14.7)	24 (20.0)	1.32 (0.71-2.44)
	Past	90 (1.8)	1 (0.8)	0.26 (0.03-2.19)
Aspirin	Current	272 (5.4)	7 (5.8)	0.63 (0.23-1.73)
	Past	55 (1.1)	1 (0.8)	0.24 (0.03-2.19)
COX-2 inhibitors	Current	40 (0.8)	—	—
	Past	58 (1.2)	3 (2.5)	2.17 (0.43-6.81)
H ₂ -blockers	Current	64 (1.3)	4 (3.3)	2.13 (0.71-6.41)
	Past	75 (1.5)	1 (0.8)	0.37 (0.05-3.03)
Lipid lowering	Current	282 (5.6)	8 (6.7)	1.31 (0.50-3.45)
	Past	25 (0.5)	2 (1.7)	8.32 (1.55-44.8)
NSAIDs	Current	293 (5.9)	6 (5.0)	0.59 (0.23-1.48)
	Past	537 (10.7)	24 (20.0)	1.61 (0.96-2.7)
Oral steroids	Current	33 (0.7)	2 (1.7)	2.21 (0.44-11.08)
	Past	37 (0.7)	2 (1.7)	0.79 (0.15-4.07)
Paracetamol	Current	335 (6.7)	12 (10.0)	1.05 (0.51-2.14)
	Past	428 (8.6)	15 (12.5)	1.15 (0.61-2.16)
PPI	Current	215 (4.3)	6 (5.0)	0.83 (0.33-2.09)
	Past	127 (2.5)	2 (1.7)	0.4 (0.09-1.83)

NSAID, Nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Statistically significant ORs are in boldface.

*Use status in relation to the date of diagnosis of anaphylaxis in cases and the index date in controls: "current," drug used in last 30 days; "past," drug used during the previous 31 to 365 days.

†Estimates adjusted by age, sex, calendar year, body mass index, previous comorbidity, and all variables in the table using an unconditional logistic regression model.

Therefore, patients with asthma should be educated about the common manifestations of anaphylaxis so that appropriate, early action may be taken on signs of their appearance.

Anaphylaxis is associated with a high risk of recurrence but is highly unpredictable. In our study, individuals with anaphylaxis were estimated to relapse at a rate of 0.06 to 0.11 episodes per person-year. The finding that the recurrence rate in patients with severe asthma compared with those without asthma is significant is interesting, although because of the limited number of events, one must be cautious in interpreting these data. Our recurrence

rate is well in line with one of the few published studies to have evaluated anaphylaxis relapse, which concluded that in any 1 year, 1 in 12 patients who have had anaphylaxis will have a recurrence and that 1 in 50 will require hospital treatment or adrenaline.²² In a large number of cases, recurrence was associated with sensitivity to wheat and/or exercise. However, the unpredictable nature of anaphylaxis does not allow for a prophylactic strategy to be implemented, although avoidance of known allergies should help maintain low levels of anaphylactic reactions.

TABLE IV. Drug use and the risk of anaphylaxis in the asthma population

Drug	Use status*	Controls (n = 5000) n (%)	Cases (n = 262) n (%)	OR† (95% CI)
Antibiotics	Current	562 (11.2)	46 (17.6)	1.61 (1.08-2.39)
	Past	2083 (41.7)	122 (46.6)	1.35 (1.01-1.80)
Antidepressants	Current	469 (9.4)	31 (11.8)	1.15 (0.75-1.75)
	Past	323 (6.5)	27 (10.3)	1.64 (1.05-2.55)
Antidiabetics	Current	153 (3.1)	9 (3.4)	0.44 (0.15-1.33)
	Past	11 (0.2)	1 (0.4)	0.44 (0.04-4.79)
Antihistamines	Current	300 (6.0)	44 (16.8)	2.92 (1.97-4.31)
	Past	519 (10.4)	43 (16.4)	1.68 (1.16-2.45)
Antihypertensives	Current	795 (15.9)	50 (19.1)	1.25 (0.81-1.94)
	Past	132 (2.6)	8 (3.1)	1.03 (0.47-2.27)
Antimuscarinics	Current	192 (3.8)	6 (2.3)	0.37 (0.15-0.87)
	Past	190 (3.8)	11 (4.2)	0.92 (0.48-1.77)
Aspirin	Current	283 (5.7)	19 (7.3)	1.23 (0.72-2.1)
	Past	71 (1.4)	7 (2.7)	1.69 (0.73-3.92)
β ₂ -Agonists	Current	1543 (30.9)	97 (37.0)	1.30 (0.85-1.99)
	Past	2070 (41.4)	105 (40.1)	1.02 (0.70-1.49)
COX-2 inhibitors	Current	31 (0.6)	5 (1.9)	2.04 (0.69-6.07)
	Past	93 (1.9)	3 (1.1)	0.46 (0.14-1.54)
Cromoglycate	Current	54 (1.1)	3 (1.1)	0.75 (0.23-2.49)
	Past	178 (3.6)	15 (5.7)	1.29 (0.73-2.27)
H ₂ -blockers	Current	101 (2.0)	4 (1.5)	0.50 (0.17-1.46)
	Past	111 (2.2)	13 (5.0)	2.06 (1.09-3.90)
Immunologic	Current	121 (2.4)	10 (3.8)	1.59 (0.80-3.15)
	Past	674 (13.5)	46 (17.6)	1.36 (0.96-1.93)
Inhaled steroids	Current	1116 (22.3)	64 (24.4)	0.95 (0.62-1.44)
	Past	1836 (36.7)	106 (40.5)	1.16 (0.83-1.63)
Lipid lowering	Current	330 (6.6)	20 (7.6)	0.77 (0.41-1.44)
	Past	35 (0.7)	2 (0.8)	0.75 (0.15-3.68)
NSAIDs	Current	307 (6.1)	25 (9.5)	1.33 (0.80-2.22)
	Past	622 (12.4)	38 (14.5)	1.24 (0.84-1.81)
Oral steroids	Current	218 (4.4)	24 (9.2)	1.96 (1.19-3.22)
	Past	669 (13.4)	42 (16.0)	1.14 (0.78-1.65)
Paracetamol	Current	508 (10.2)	35 (13.4)	1.08 (0.70-1.66)
	Past	718 (14.4)	43 (16.4)	1.04 (0.72-1.50)
PPI	Current	309 (6.2)	23 (8.8)	1.03 (0.62-1.73)
	Past	163 (3.3)	9 (3.4)	0.84 (0.41-1.72)
Theophylline	Current	109 (2.2)	11 (4.2)	1.93 (0.96-3.91)
	Past	65 (1.3)	2 (0.8)	0.42 (0.10-1.83)

NSAID, Nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

Statistically significant ORs are in boldface.

*Use status in relation to the date of diagnosis of anaphylaxis in cases and the index date in controls: "current," drug used in last 30 days; "past," drug used during the previous 31 to 365 days.

†Estimates adjusted by age, sex, calendar year, body mass index, previous comorbidity, and all variables in the table using an unconditional logistic regression model.

Several potential limitations of our study should be noted. First, the list of nonspecific codes that we reviewed was not exhaustive, and additional cases of anaphylaxis might have been identified by including a broader range of codes (eg, 989.82, "toxic effect of latex," or 995.2, "unspecified adverse effect of drug, medicinal, and biological substance"). It has been reported that 47% of patients with food allergy and 13% with insect sting allergy would have been missed using specific ICD-9-M codes alone.²³ Using a broader range of codes would not change the incidence estimate based on the specific codes but might increase the estimate based on all diagnoses. Second, a large number of exploratory hypotheses were tested, with no adjustment for multiple testing, and any significant results in this study would need to be replicated in an independent study. Third, there was a lack of consensus among GPs on a standard case definition—almost identical cases were considered to be anaphylaxis by some practitioners but not by others. Related to this is the lack of any consistent diagnosis of anaphylaxis. Previous studies of anaphylaxis found that cases of

anaphylaxis were coded as a variety of other conditions.^{10,11} Although thorough investigation of these other codes does appear to be important for complete capture of anaphylaxis (and description of the true incidence), their high frequency and low predictive value present a logistical challenge. In an attempt to overcome this potential limitation, we reviewed all medical records for those codes thought to be related to anaphylaxis, but we cannot discount the possibility that some cases of anaphylaxis may not have been recorded by the GPs, especially if the event occurred in the hospital. Nevertheless, it has been consistently demonstrated that the THIN database contains data of excellent quality and completeness.⁷

To assess how the different criteria in GP diagnosis might influence our study results, we ran a sensitivity analysis in which only cases with a specific diagnosis of anaphylactic shock requiring immediate emergency treatment were included. This group represents a homogeneous subset of cases of severe anaphylaxis involving a multisystem allergic reaction. This

TABLE V. Causes, symptoms, and consequences of anaphylaxis

	Total (n = 382) n (%)	No asthma (n = 120) n (%)	Severe asthma (n = 78) n (%)	Nonsevere asthma (n = 184) n (%)
Anaphylaxis cause*				
Drug	102 (27)	29 (24)	27 (35)	46 (25)
Food	92 (24)	19 (16)	18 (23)	55 (30)
Insect	46 (12)	15 (13)	11 (14)	19 (10)
Latex	3 (0.78)	0	1 (1)	2 (1)
Anaphylaxis of unknown cause	103 (27)	37 (31)	17 (22)	49 (27)
No information/other	37 (10)	20 (17)	4 (5)	13 (7)
Anaphylaxis symptoms				
Cutaneous	287 (75)	96 (80)	57 (73)	134 (73)
Respiratory	120 (31)	18 (15)	36 (46)	66 (36)
Cardiovascular	39 (10)	10 (8)	11 (14)	18 (10)
Gastrointestinal	17 (4)	4 (3)	5 (6)	8 (4)
Other	16 (4)	7 (6)	3 (4)	6 (3)
No information/other	52 (14)	16 (13)	10 (13)	26 (14)
Health care resource use				
Hospitalization or A&E visit	188 (49)	56 (47)	40 (51)	92 (50)
Outpatient visit	58 (15)	20 (17)	11 (14)	27 (15)
Neither	115 (30)	36 (30)	22 (28)	57 (31)
No information	21 (6)	8 (7)	5 (6)	8 (4)

A&E, Accident and emergency department.

*Valid cases = 382 (1 case might have various suspected causes).

analysis yielded risk estimates fully consistent with those from our main analyses, suggesting that the studied risk factors of anaphylaxis are not different in this subset of cases and share a similar magnitude of effect.

In conclusion, patients with asthma have a greater risk of anaphylaxis than those without asthma, with the risk greater in severe than nonsevere asthma. In addition, we found that women are at higher risk of anaphylaxis than men, especially if they have severe asthma. Consistent with previous studies, we found that drugs and foods are the most frequent causes of anaphylaxis. The majority of anaphylactic episodes result in the individual being hospitalized, visiting an accident and emergency department, or being seen as an outpatient.

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Clinical implications: Physicians should consider anaphylaxis risk factors including sex, comorbidities, and concomitant medications, along with the need for increased education among at-risk patients, such as those with asthma.

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Anaphylaxis Questionnaire

Practice ID	Patient ID	Sex	Age (at date of Event)	Date of Event

Please answer all the questions according to the information held in the patient's written records by ticking the appropriate box or writing in the space provided.

If the patient has transferred out or died please try to complete the questionnaire from memory

This form was completed: using records ☐ from memory ☐ (please tick)

1. Could you please confirm if this patient experienced his/her FIRST episode of ANAPHYLAXIS around the above mentioned date?					
☐ Yes ☐ No Please specify the date if different from the above mentioned? _____					
2. What signs and/or symptoms did the patient experience during this episode of anaphylaxis? (more than one alternative possible)					
		Yes	No		Yes No
Cardiovascular symptoms		☐	☐	Respiratory symptoms	☐ ☐
reduced blood pressure		☐	☐	dyspnoea	☐ ☐
cardiovascular collapse		☐	☐	wheeze/bronchospasm	☐ ☐
other: _____		☐	☐	stridor	☐ ☐
				reduced peak expiratory flow	☐ ☐
		Yes	No	other: _____	☐ ☐
Cutaneous symptoms		☐	☐	Gastrointestinal symptoms	☐ ☐
hives		☐	☐	Other	☐ ☐
generalised itch/flush		☐	☐	Please specify: _____	
swollen lips/tongue/uvula		☐	☐		
other: _____		☐	☐		
3. In your opinion what was the most likely cause of this episode?					
☐ Drug-induced anaphylaxis. Please specify: _____ ☐ Anaesthetic-induced anaphylaxis ☐ Insect-sting induced anaphylaxis ☐ Food-induced anaphylaxis ☐ Latex-induced anaphylaxis ☐ Exercise-induced anaphylaxis ☐ Idiopathic anaphylaxis					
4. Did the episode of anaphylaxis require any of the following? (Tick all that apply)					
		Yes	No		
Outpatient visit		☐	☐		
A&E/casualty dept. visit		☐	☐		
Hospital admission		☐	☐		
5. After this first episode, has this patient experienced new episodes of anaphylaxis? Yes ☐ No ☐					
If Yes, please specify how long after the first episode? Less than 72 hours ☐ More than 72 hours ☐					

FIG E1. Potential cases of anaphylaxis were validated by contacting patients' GPs, who were asked to complete an anaphylaxis questionnaire.