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REVIEW ARTICLE

The epidemiology of anaphylaxis in Europe: a systematic review

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Abstract

Background: Anaphylaxis is an acute, potentially fatal, multi-organ system, allergic reaction caused by the release of chemical mediators from mast cells and basophils. Uncertainty exists around epidemiological measures of incidence and prevalence, risk factors, risk of recurrence, and death due to anaphylaxis. This systematic review aimed to (1) understand and describe the epidemiology of anaphylaxis and (2) describe how these characteristics vary by person, place, and time.

Methods: Using a highly sensitive search strategy, we identified systematic reviews of epidemiological studies, descriptive and analytical epidemiological investigations, and studies involving analysis of routine data.

Results: Our searches identified a total of 5 843 potentially eligible studies, of which 49 satisfied our inclusion criteria. Of these, three were suitable for pooled estimates of prevalence. The incidence rates for all-cause anaphylaxis ranged from 1.5 to 7.9 per 100 000 person-years. These data indicated that an estimated 0.3% (95% CI 0.1–0.5) of the population experience anaphylaxis at some point in their lives. Food, drugs, stinging insects, and latex were the most commonly identified triggers.

Conclusions: Anaphylaxis is a common problem, affecting an estimated 1 in 300 of the European population at some time in their lives. Future research needs to

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Anaphylaxis is a 'severe, life-threatening, generalized or systemic hypersensitivity reaction'. Several working definitions of anaphylaxis have been formulated to aid diagnosis and management (1–4). The most well known is the consensus clinical definition proposed by Sampson et al., which involved representatives of a number of international allergy organizations, including the European Academy of Allergy and Clinical Immunology (EAACI) (Box 1) (5).

With anaphylaxis being a syndrome with variable symptoms, signs, and timecourse, none of the definitions are ideal and impede accurate epidemiological study (6). Additionally, the acute onset and transient nature render it difficult to mount prospective investigations (7). Notwithstanding these inherent challenges, there is a need to improve our understanding of the epidemiology of anaphylaxis to understand the overall disease burden posed by the condition and obtain insights into its etiology, risk stratification, and prognosis. Epidemiological measures of particular interest for anaphylaxis therefore include measures of incidence and prevalence, risk factors, and risk of recurrence and death (8) (Box 2). Other aspects of interest concern features of persons who experience anaphylaxis, temporal relationships, and the factors that lead to its development and recurrence (9).

The EAACI is developing *EAACI Guidelines for Food Allergy and Anaphylaxis*, and this systematic review is one of seven interlinked evidence syntheses that have been undertaken to provide a state-of-the-art European synopsis of the current evidence base in relation to epidemiology, prevention, diagnosis and clinical management, and impact on quality of life, which will be used to inform clinical recommendations.

Aims

The aims of this systematic review were to (1) understand and describe the epidemiology of anaphylaxis, that is, frequency, risk factors, and outcomes of anaphylaxis and (2) describe how these characteristics vary by person, place, and time.

Methods

The protocol of this review has been published previously (10), and it is registered with the International Prospective Register of Systematic Reviews (PROSPERO; http://www.crd.york.ac.uk/prospero/, reference CRD42013003702).

Box 1: Clinical criteria for diagnosing anaphylaxis

Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled

(1) Acute onset of an illness (minutes to hours) with involvement of
- Skin/mucosal tissue (e.g., hives, generalized itch/flush, swollen lips/tongue/uvula)
- AND
- Airway compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
- OR
- Reduced BP or associated symptoms (e.g., hypotonia, syncope)

(2) Two or more of the following after exposure to known allergen for that patient (minutes to hours)
- History of severe allergic reaction
- Skin/mucosal tissue (e.g., hives, generalized itch/flush, swollen lips/tongue/uvula)
- Airway compromise (e.g., dyspnea, wheeze/bronchospasm, stridor, reduced PEF)
- Reduced BP or associated symptoms (e.g., hypotonia, syncope)
- In suspected food allergy: gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

(3) Hypotension after exposure to known allergen for that patient (minutes to hours)
- Infants and children: low systolic BP (age-specific) or >30% drop in systolic BP*
- Adults: systolic BP <100 mm Hg or >30% drop from their baseline

Reproduced with permission from Sampson et al. (5) (C). BP, blood pressure; PEF, peak expiratory flow.
*Low systolic BP for children is defined as <70 mm Hg from 1 month to 1 year; <70 mm Hg + [2 × age] from 1 to 10 years; and <90 mm Hg from age 11–17 years.

Abbreviations

CASP, Critical Appraisal Skills Programme; EAACI, European Academy of Allergy and Clinical Immunology; EPHPP, Effective Public Health Practice Project; OR, odds ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews.

Box 2: Epidemiological definitions

Incidence: The number of new cases of anaphylaxis that occur during a given period in a defined population. Incidence will be studied as:

- Incidence rate: The number of new cases of anaphylaxis that occur during a defined period per unit person-time.
- Cumulative incidence: The number of new cases of anaphylaxis that occur during a given period per the population at risk.

Prevalence: The proportion of a defined population known to have experienced anaphylaxis. Care is required in defining the appropriate denominator. This epidemiological measure will be further divided into

- Point prevalence: the proportion of the population that has experienced anaphylaxis at a specific time
- Period prevalence: the proportion of the population that has experienced anaphylaxis during a given period
- Lifetime prevalence: the proportion of the population that at some point in their life will have experienced anaphylaxis.

Case fatality rate: The proportion of cases of anaphylaxis that proves fatal (usually defined within a time period). This is also sometimes known as the case fatality ratio.

Definitions based on those proposed by Last (9).

Search strategy

A highly sensitive search strategy was designed (see Boxes S1–4) to retrieve all articles combining the concepts of anaphylaxis and epidemiology from electronic bibliographic databases. We conceptualized the search to incorporate the three elements below as shown in Figure 1.

Inclusion criteria for study design

The following studies were included: systematic reviews ± meta-analyses, cohort studies, cross-sectional studies, case–control studies, and routine healthcare studies. These were chosen to ensure that the highest levels of evidence were pooled based on the aims of this review (11).

Exclusion criteria for study design

Reviews, discussion papers, nonresearch letters and editorials, case studies, and case series plus animal studies were excluded.

Study selection

The titles of the retrieved articles were checked independently by two reviewers (SSP and DdS) according to the selection criteria and categorized as included, not included, and unsure. The abstracts of unsure category papers were retrieved, and they were recategorized after discussion. Any discrepancies were resolved by consensus, and if necessary, a third reviewer (AS) was consulted to arbitrate. Full-text copies of potentially relevant studies were obtained and their eligibility for inclusion assessed.

Quality assessment strategy

Each study was quality-assessed independently by two reviewers (SSP and HH) using the relevant version of the Critical Appraisal Skills Programme (CASP) quality assessment tool for systematic reviews (12), cohort studies (13), and case–control studies (14), which involved an assessment of internal and external validity (15). Similarly, we used the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for assessing other forms of quantitative studies such as cross-sectional studies and routine healthcare studies (16). Any discrepancies were resolved by discussion or, where necessary, by arbitration by a third reviewer (AS).

Analysis, data synthesis, and reporting

Data were independently extracted onto a customized data extraction sheet by two reviewers (DdS and SSP), and any discrepancies were resolved by discussion or, were necessary, by arbitration by a third reviewer (AS). A descriptive summary with data tables was produced to summarize the literature. Meta-analysis was undertaken using random-effects modeling and adopting methods suggested by Agresti and Coul. Heterogeneity was assessed using Cochrane's Q, a

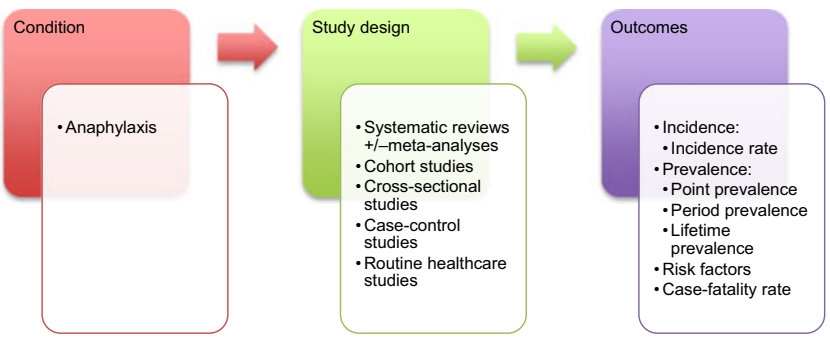

Figure 1 Conceptualization of systematic review of the epidemiology of anaphylaxis.

statistic based on the chi-square test with corresponding Z- and p-values. As this test is known to have low power, the chi-square statistic was also calculated: a value of 25% corresponds to low heterogeneity, 50% to moderate, and 75% to high (17). Comprehensive meta-analysis (Biostat, Englewood, NJ, USA) was used for these analyses. A narrative synthesis of the data was also undertaken. The PRISMA checklist was used to guide the reporting of the systematic review (see Box S5) (18).

Results

Overview of results

The searches identified a total of 5 843 potentially eligible studies, of which 49 satisfied our eligibility criteria and were therefore included in this review (see Figure 2) (19–67). The key characteristics and main findings of all included studies are detailed in Table S1, and the quality assessment of these studies is summarized in Table S2. The main findings are further discussed in more detail below.

Incidence, prevalence, and trends over time

Incidence

Ten studies offered varying estimates of incidence rates as shown in Table S1 (24, 31, 44, 50–52, 56–59). These ranged from 1.5 per 100 000 person-years (24) to 32 per 100 000 person-years (45). In one study, over a 4-year period, anaphylaxis was the cause of 0.1% of children's hospital admissions and 0.3% of adult admissions (50). Pooled analysis was not possible due to the heterogeneity of the populations and the different approaches to reporting incidence in these studies.

Prevalence

The descriptions used in studies typically failed to differentiate clearly between measures of point, period, and lifetime prevalence. Quantitative data were available for pooling from three population-based studies (26, 39, 57); in which estimates of prevalence ranged from 1 of 1333 (0.1%) (57) to 37 of 6676 (0.6%) (39). Meta-analysis ($I^2 = 99.9\%$) yielded a pooled prevalence estimate of 0.3% (95% CI 0.1–0.5), as shown in Figure 3.

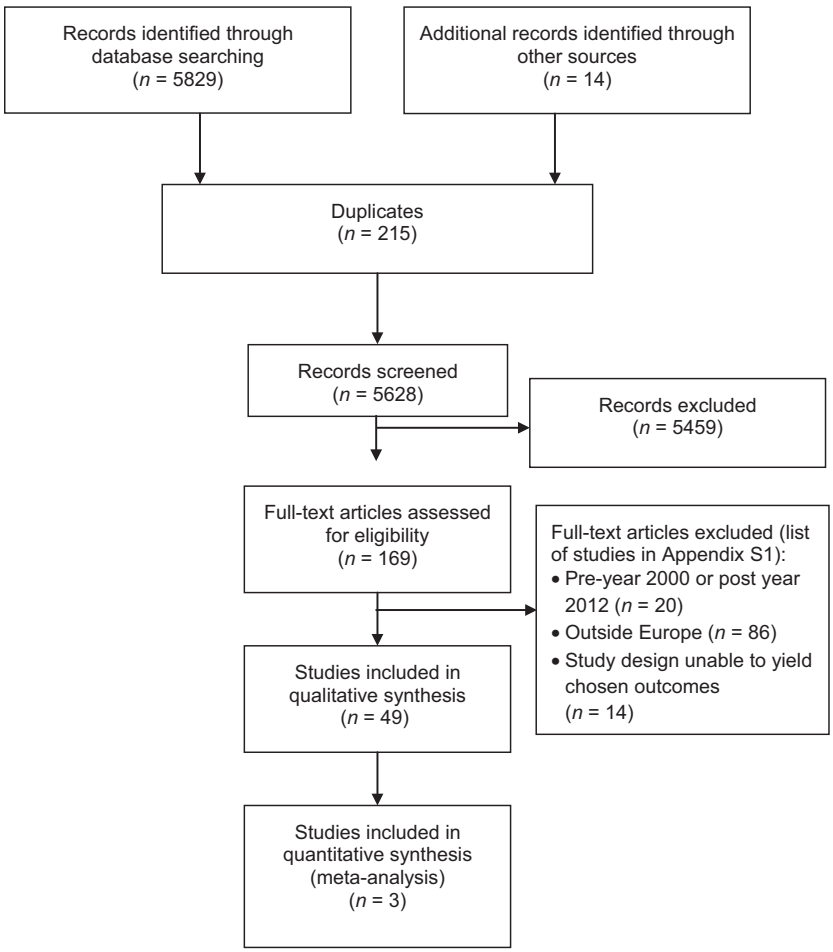

Figure 2 PRISMA diagram for epidemiology of anaphylaxis.

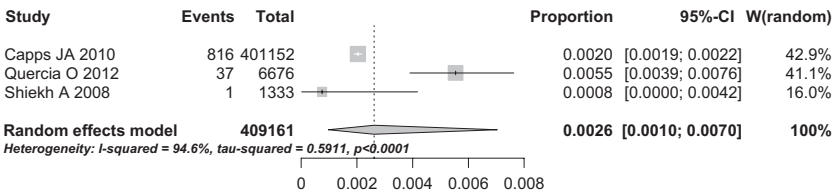

Figure 3 Pooled estimate for the prevalence of anaphylaxis.

Variations by person, place, and time

Person

In a study of 325 046 people, a peak incidence of 313.58 per 100 000 person-years was noted in the 0- to 4-year-old group; this was significantly different ($P < 0.05$) to other age groups. For affected people over 10 years of age, incidence tended to be higher for females (58). A review of 816 of 401 152 (0.2%) ambulance calls for anaphylaxis found that 180 of 816 (22%) involved children (26). Secondary analyses of various healthcare databases found that 4.1 per 100 000 admissions to hospitals were in the 0–14 years group, 3.9 per 100 000 in the 15–44 years group, and 3.5 per 100 000 in the 45 years and older group (52).

Place

The study by Sheikh et al. reviewed 13.5 million emergency hospital admissions (2 323 for anaphylaxis) over a 5-year period. A north–south divide existed in the UK with a higher frequency of anaphylaxis admissions in the south (rate ratio 1.35, 95% CI 1.25–1.47). A rural to urban rate ratio of 1.35 (95% CI 1.17–1.59) and a nondeprived to deprived rate ratio of 1.32 (95% CI 1.19–1.46) were also noted (56).

Time

Increases in the incidence rate of anaphylaxis have been reported (44, 51, 57). The incidence of hospital admissions for anaphylaxis increased from 5.6 per 100 000 discharges in 1991–92 to 10.2 per 100 000 discharges in 1994–95 (44). Age–sex standardized incidence was estimated as 6.7 per 100 000 person-years in 2001, rising to 7.9 per 100 000 person-years in 2005 (57). Anaphylaxis rates rose from 6 to 41 per million admissions between 1990–91 and 2000–01 (51). On a similar note, the lifetime age–sex standardized prevalence of recorded diagnosis of anaphylaxis was 50 per 100 000 in 2001, rising to 75.5 per 100 000 in 2005 (57).

Triggers (elicitors) and comorbidities

The key triggers identified in these studies included foods, medications, stinging insects, and latex. Comorbidities such as atopic eczema/dermatitis and asthma were also found to be important (30). For example, in a case–control study of coexisting asthma, atopic eczema/dermatitis was the only factor associated with a significantly increased risk of anaphylaxis within the asthma-free cohort (odds ratio (OR) 2.83, 95% CI 1.51–5.29). Within the cohort with asthma, the following comorbidities were associated with increased occurrence of anaphylaxis: allergic rhinitis (OR 1.76, 95% CI 1.35–2.30), atopic eczema/dermatitis (OR 1.69, 95% CI 1.13–2.51), and osteoarthritis (OR 1.50, 95% CI 1.05–2.14) (30).

Food-triggered reactions

The proportions of food allergy reactions that resulted in anaphylaxis varied markedly (28, 32, 41, 46, 64, 67) with estimates ranging from 12 of 2716 (0.4%) (41) to 65 of 163 (39.9%) (Table S1) (64). Different estimates of the most frequent food allergens implicated in anaphylaxis have been provided by the studies. For example, peanuts and tree nuts (27.6%), hen's egg (8.6%), and foods cross-reacting with latex (11%) were the most commonly identified food triggers in one study (64). The food allergens that most commonly resulted in anaphylaxis in another study of 163 children were cow's milk (47 of 163, 29%), hen's egg (25 of 163, 25%), hazelnut (9 of 163, 5%), peanut (6 of 163, 4%), kiwi (7 of 163, 4%), walnut (6 of 163, 4%), pine nut (5 of 163, 3%), fish (5 of 163, 3%), wheat (4 of 163, 2%), soy (3 of 163, 2%), shrimp (3 of 163, 2%), apricot (3 of 163, 2%), and sesame (3 of 163, 2%) (28). Exposure to airborne allergens increased the risk of anaphylaxis due to food with children with pollen allergy being at increased risk of being admitted with food-related anaphylaxis during the pollen season (46).

Medication- and therapeutic agent-triggered reactions

The systematic review by Nybo et al. (2008) (36) included 25 studies, only two of which met our inclusion criteria (35, 54). Five studies provided estimates for medication-triggered anaphylaxis (22, 23, 33, 36, 48, 68), which ranged from 3 of 1446 (0.2%) (33) to 3 of 96 3.1% (22). There was wide variation in the frequency of anaphylaxis associated with different medications. For example, the rate per 100 000 exposed cases was 2.1 for aspirin, 32.0 for parenteral penicillin, and 378.0 for parenteral plasma. These plasma reactions are considered to be infusion reactions rather than true cases of anaphylaxis. There was a relatively low risk for dipyrone, diclofenac, paracetamol, ampicillin, cloxacillin, and cephalosporins. In contrast, parenteral penicillin, dextran, contrast media, blood, and pentoxifylline were associated with intermediate risks. The highest incidences were observed in those receiving plasma and streptokinase (34). However, given the diverse nature of the studies, it is difficult to make conclusions on the true frequency of anaphylaxis in this category.

Stinging insect-triggered reactions

One study found that 6.5% of beekeepers had a systemic reaction to beesting in the past 12 months; 9 of 494 (2%) of these reactions resulted in anaphylaxis (27). The risk of systemic

reactions increased when atopic disease was present: seasonal allergic rhinitis (OR 4.4, 95% CI 1.2–11.5), perennial rhinitis (OR 4.6, 95% CI 1.2–18.2), food allergy (OR 7.0, 95% 2.0–25.0), physician-diagnosed asthma (OR 8.0, 95% CI 2.5–25.6), and any atopic disease (OR 10.9, 95% CI 3.5–33.8).

Latex-triggered reactions

Focusing on pregnant women undergoing surgery in hospital, 2 of 588 (0.34%) experienced anaphylaxis due to latex allergy (29).

Prognosis

Case fatality rates were noted in three studies at 0.000002% (52), 0.00009% (56), and 0.0001% (31).

Studies in progress

We are aware of one study in progress which is investigating the epidemiology and healthcare utilization in children and adults with anaphylaxis in Denmark; this is expected to report later in 2013.

Discussion

Summary of main findings

The population-based incidence of anaphylaxis in Europe is estimated at 1.5–7.9 per 100 000 person-years (57). There is some evidence that the incidence of anaphylaxis may be increasing, but this may be due to changing clinical definitions or thresholds for presentation or admission. Studies would suggest that approximately 0.3% (95% CI 0.1–0.5) of the European population have experienced anaphylaxis at some point in their lives. These figures vary by age, geographical regions, and exposure. They also depend on the source of data, for example, historical medical records, national databases and data collected by general practitioners or specialists, and the definitions used (69). It was beyond the scope of this review to ascertain these factors. This review has also found that foods, drugs/therapeutic agents, stinging insects, and latex are the most common triggers of anaphylaxis. Overall, the case fatality ratio from anaphylaxis was low, estimated at under 0.0001%.

Strengths and limitations

This is, as far as we are aware, the first systematic review of the epidemiology of anaphylaxis in European populations. Key strengths of this work include searches of a range of relevant databases, independent critical appraisal of studies, and, where appropriate, quantitative synthesis of data.

Our systematic review does not include studies prior to 2000 and is limited to Europe; this review may therefore not be generalizable to non-European settings. For example, it has excluded a recent epidemiological investigation from Turkey consisting of 114 patients hospitalized due to anaphylaxis over a 1-year period giving a lifetime prevalence of 1.95 per 100 000 person-years (95% CI 1.30–3.77) (68). The varying estimates of epidemiological frequency are likely to be due to varying study designs, approaches, and definitions used by the authors. It was beyond the scope of this review to ascertain severity of anaphylaxis; milder systemic reactions that are successfully treated by self-medication may never be captured, and this could result in an underestimate of our figures. Most of the studies reviewed relied on the clinical history along with sensitization for case finding. Experience with challenge testing has shown that there will be an overestimation of prevalence in studies using this method of case finding. While this may suggest transient forms of anaphylaxis, there may also be other unrecognized pathology accounting for symptoms in an unknown number of cases.

Interpreting findings in the context of the wider literature

A review by a Working Group of the American College of Allergy, Asthma, and Immunology summarized the findings from some principal studies published in English. Most of these were outside the time period of interest and included a number of non-European studies. This Working Group concluded that the overall incidence of anaphylaxis was between 30–60 cases per 100 000 person-years and 950 cases per 100 000 person-years, with a lifetime prevalence 0.05–2.0%. Even the higher figure could be an underestimate due to underdiagnosis and under-reporting (6). There may also be factors associated with poor diagnosis by nonspecialists in allergy (70). Our pooled estimates are somewhat lower, although the range is very wide, perhaps reflecting differences in diagnostic criteria for anaphylaxis between Europe and North America.

Implications for research, policy, and practice

The occurrence of anaphylaxis can have a profound effect on the quality of life of the sufferer and their family (71). The risk of recurrence may be high, and some attacks prove fatal. Successfully identifying those at greatest risk of an initial attack, and a recurrence, could reduce morbidity, but this has proved difficult in practice using demographic and clinical markers. Genetic factors may have the potential to help fill this gap by identifying those at particularly high risk of severe reactions.

Secondary analyses of routine sources of data have proved helpful in describing the epidemiology of anaphylaxis, although the estimates generated would be considered more reliable if the data could be validated and linked across primary and secondary care sectors (72). Such validation work needs to be prioritized. Vigilance is needed as new drugs or foods are introduced. National reporting systems of adverse drug reactions or adverse reactions to foods associated with anaphylaxis may need reinforcing, perhaps through the use of prompts during patient consultations.

Conclusions

Improved data capture in and across routine health databases is required if we are to obtain more accurate estimates of the burden of anaphylaxis. This may be obtained through

agreement on an acceptable definition of anaphylaxis (73) use of standard coding conventions (e.g., ICD-10, SNOMED-CT). At present, the best epidemiological estimates appear to come from north-west Europe, but more information is needed from southern and eastern Europe.

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Author contributions

AS, AM, and GR conceived this review. It was undertaken by SSP with the support of SJ and DdS. SSP and AS led the drafting of the manuscript, and all authors critically commented on drafts of the manuscript.

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Conflicts of interest

None.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Search strategies.

Box S1. Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1990 to Present>.

Box S2. Database: Embase Classic+Embase <1990 to 2012 August 19>.

Box S3. Database: CINAHL via Ebsco.

Box S4. Database: ISI Web of Science: Science Citation Index, Conference Proceedings Citation.

Box S5. PRISMA Checklist.

Table S1. Key characteristics of included studies

Table S2. Quality scoring of studies.

Appendix S1: Reasons for excluding studies.

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