

REVIEW ARTICLE

The epidemiology of anaphylaxis in Europe: a systematic review

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Keywords

anaphylaxis; epidemiology; incidence; prevalence; risk factors.

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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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focus on better understanding of the trends across Europe and identifying those most likely to experience fatal reactions.

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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/prospéro/>, 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).

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, where 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

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 $\pm$ 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).

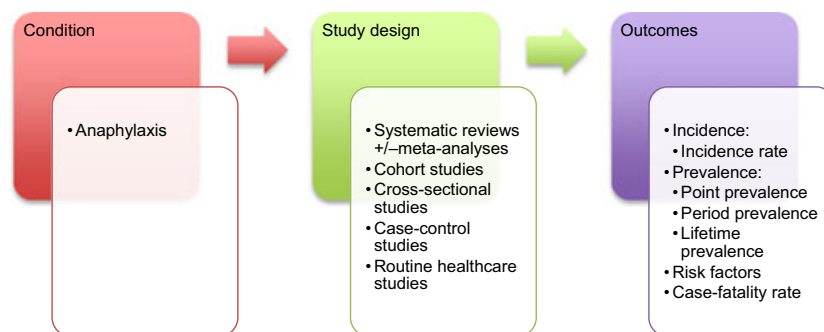


Figure 1 Conceptualization of systematic review of the epidemiology of anaphylaxis.

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.

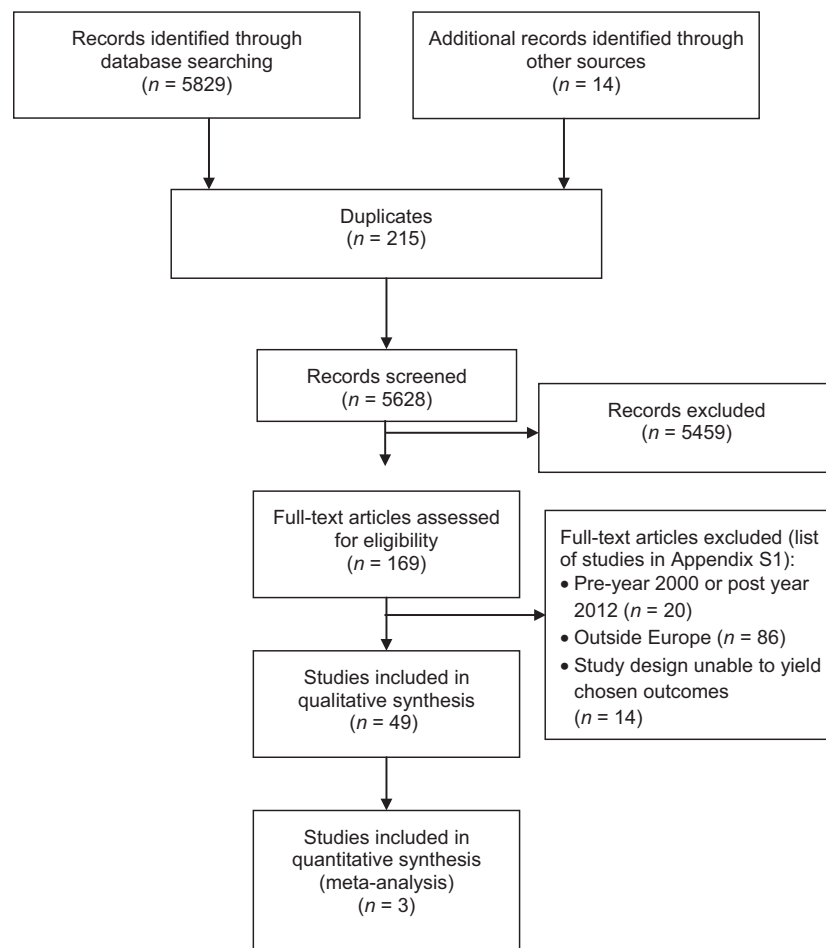


Figure 2 PRISMA diagram for epidemiology of anaphylaxis.

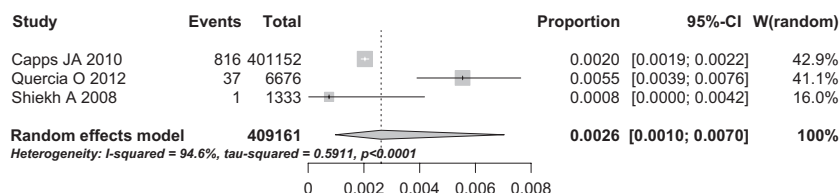


Figure 3 Pooled estimate for the prevalence of anaphylaxis.

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 beekeeping 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% CI 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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Long title: The epidemiology of anaphylaxis in Europe: a systematic review

Short title: Epidemiology of anaphylaxis in Europe

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Search strategies

To retrieve systematic reviews, we used the systematic review filter developed at McMaster University Health Information Research Unit (HIRU; http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Reviews). We also adapted the search filter from York University Centre for Reviews and Dissemination (http://www.york.ac.uk/inst/crd/intertasc/epidemiological_studies.html) to retrieve incidence, prevalence, and other characteristics describing the epidemiology of anaphylaxis. Similarly, we also applied the McMaster filter for prognosis studies (http://hiru.mcmaster.ca/hiru/HIRU_Hedges_EMBASE_Strategies.aspx#Prognosis).

The following databases were searched: MEDLINE (OVID), Embase (OVID), CINAHL (Ebscohost) and ISI Web of Science (Thomson Web of Knowledge). The search strategy was devised on OVID MEDLINE and then adapted for the other databases (see Boxes E1-4). In all cases, the databases were searched from January 1, 2000 to September 30, 2012. Searches were limited to literature from 2000 onwards because we wanted to understand and describe the contemporary epidemiology of anaphylaxis, and ensure a pragmatic approach to dealing with the vast body of literature. Given the scope of the European guidelines, the search was limited to European evidence. European countries were based on the definitions provided by the Organisation for Economic Co-operation and Development (OECD) (<http://www.oecd.org/std/oecdmaineconomicindicators-countriescovered.htm>), i.e. Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom (UK). All references were collated into an EndNote Library and tagged with the name of the database. Additional references were located through searching the references cited by the identified studies, and unpublished work, and research in progress was identified through discussion with experts in the field. We also invited experts who are active in the field from a range of disciplines and geography to comment on our search strategy, and the list of included studies. There were no language restrictions and, where possible, all literature was translated.

Box E1: Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1990 to Present>

Search Strategy:

- 1 Anaphylaxis/
- 2 anaphylaxis react*.mp.
- 3 anaphylactic react*.mp.
- 4 anaphylactic shock*.mp.
- 5 anaphylactoid syndrome*.mp.
- 6 anaphylactoid react*.mp.
- 7 anaphylactic syndrome*.mp.
- 8 anaphylactoid shock*.mp.
- 9 acute systemic allergic react*.mp.
- 10 idiopathic anaphylaxis.mp.
- 11 systemic anaphylaxis.mp.
- 12 or/1-11
 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine
- 13 or animal\$.ti.
- 14 exp animals/ not humans.sh.
- 15 13 or 14
- 16 12 not 15
- 17 *Incidence/
- 18 *Prevalence/
- 19 (incidence or prevalence or epidemiol\$).ti.
- 20 epidemiologic methods/
- 21 *cohort studies/
- 22 controlled clinical trial.pt.
- 23 *case-control studies/
- 24 exp Anaphylaxis/ep [Epidemiology]
- 25 exp Hospitalization/
- 26 exp Hospitalization/sn, td [Statistics & Numerical Data, Trends]
- 27 exp Mortality/sn, td [Statistics & Numerical Data, Trends]
- 28 exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy]
- 29 exp "Cause of Death"/
- 30 ((adrenaline or epinephrine) adj3 (dispens\$ or prescrib\$)).tw.
- 31 or/17-30
- 32 16 and 31
- 33 limit 32 to yr="1990 - 2012"

Box E2: Database: Embase Classic+Embase <1990 to 2012 August 19>

Search Strategy:

- 1 Anaphylaxis/
- 2 anaphylaxis react*.mp.
- 3 anaphylactic react*.mp.
- 4 anaphylactic shock*.mp.
- 5 anaphylactoid syndrome*.mp.
- 6 anaphylactoid react*.mp.
- 7 anaphylactic syndrome*.mp.
- 8 anaphylactoid shock*.mp.
- 9 acute systemic allergic react*.mp.
- 10 idiopathic anaphylaxis.mp.
- 11 systemic anaphylaxis.mp.
- 12 or/1-11
(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine
- 13 or animal\$.ti.
- 14 exp animals/ not humans.sh.
- 15 13 or 14
- 16 12 not 15
- 17 *Incidence/
- 18 *Prevalence/
- 19 (incidence or prevalence or epidemiol\$.ti.
- 20 epidemiologic methods/
- 21 *cohort studies/
- 22 controlled clinical trial.pt.
- 23 *case-control studies/
- 24 exp Anaphylaxis/ep [Epidemiology]
- 25 exp Hospitalization/
- 26 exp Hospitalization/sn, td [Statistics & Numerical Data, Trends]
- 27 exp Mortality/sn, td [Statistics & Numerical Data, Trends]
- 28 exp Epinephrine/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy]
- 29 exp "Cause of Death"/
- 30 ((adrenaline or epinephrine) adj3 (dispens\$ or prescrib\$)).tw.
- 31 or/17-30
- 32 16 and 31
- 33 limit 32 to yr="1990 - 2012"

Box E3: Database: CINAHL via Ebsco

Search strategy:

#	Query
S16	S11 and S15
S15	S12 or S13 or S14
S14	(MM "Anaphylaxis")
S13	"anaphylactic shock"
S12	"anaphylactic"
S11	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
S10	(MM "Prevalence")
S9	(MH "Incidence")
S8	(MH "Prescribing Patterns")
S7	"Epinephrine prescription"
S6	"Epinephrine dispensing"
S5	(MH "Epinephrine/AD/SD")
S4	(MH "Epinephrine")
S3	(MM "Hospitalization")
S2	(MM "Disease Surveillance")
S1	(MH "Epidemiology") OR (MH "Epidemiological Research")

Box E4: Database: ISI Web of Science: Science Citation Index, Conference Proceedings

Citation

Search strategy:

4 #2 AND #1

Refined by: Web of Science Categories=(ALLERGY OR IMMUNOLOGY OR MEDICINE
GENERAL INTERNAL) AND Publication Years=(1990-2012) AND Document Types=(
PROCEEDINGS PAPER OR REVIEW OR MEETING ABSTRACT)

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years

Lemmatization=On

3 #2 AND #1

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years

Lemmatization=On

2 Topic=((epidemiol* or incidence or prevalance or surveillance or death or mortality or survival or
prescrib* or prescript*))

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years

Lemmatization=On

1 Topic=(anaphylaxis or anaphylactic)

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years

Lemmatization=On

Table E1: Key characteristics of included studies

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Alvarado MI 2006 ¹	Cross-sectional	506 adults and 168 children, 106 of whom had food allergy	Allergy unit	Children 0-14 years and adults 15+	Food allergy	Self-report survey Skin prick test Blood test	Period prevalence (May 2002 to October 2004)	9.1% of participants had food allergy. 14.2% of those with food allergy had anaphylaxis. This was one of the top three symptoms of food allergy. Foods most frequently involved in anaphylaxis were tree nuts in adults and legumes and eggs in children. There were no deaths from anaphylaxis.		15/674 (2.2%)		Food		Weak
Asero R 2009 ²	Cross-sectional	1110 adults with food allergy	19 allergy centres	12-79 years, mean 31 years	Food-induced anaphylaxis	Skin prick test, blood test, medical record review	Period prevalence (1st January 2007 to 31st December 2007) Risk factors	58 out of 1110 people diagnosed with food allergy in a one year period experienced at least one episode of food induced anaphylaxis (5%). The mean age of those experiencing anaphylaxis was higher than the mean age of the general population with food allergy. Anaphylaxis was most prevalent in		58/1110 (5.2%)		Age Allergy type	Geographic area	Weak

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								people allergic to lipid transfer protein, shrimp, tree nuts, legumes other than peanuts and seeds.						
Calvani M 2011 ³	Cross-sectional	163 children with complete records out of 237	29 outpatient allergy clinics	Median 4 years, range 0-18 years	Food induced anaphylaxis	Self-report survey Skin-prick test	Risk factors	36 foods were reported causes of anaphylaxis. Cow's milk was the most common, responsible for 29% of anaphylaxis reports. Half of cow's milk reactions occurred in those under two years. Egg was responsible for 15% of anaphylaxis and was also most common in those under two years. Most cow's milk related anaphylaxis was moderate whereas most egg induced anaphylaxis was severe. Neither age nor gender was associated with severity. Clinical history of asthma or gastrointestinal symptoms and allergy to peanut.				Food Exercise	Age Gender Previous episodes Conditions Family history	Moderate

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								egg, pine nut, cow's milk and walnut were associated with severity.						
Derby CJ 2005 ⁴	Cross-sectional	400 surveys sent, 280 surveys returned, 257 surveys of adults and children valid	Members anaphylaxis charity who avoided sesame	N/A	Sesame allergy	Self-report survey	Point prevalence (April 2002) Risk factors Outcomes	18% reported anaphylaxis as a reaction to sesame. 89% of people who reacted to sesame reported other atopic conditions. 91% reported other food allergies. 10% of first reactions, which usually happened in children, were potentially life threatening. 18% reported anaphylaxis due to sesame.		27/150 (18%)		Food	Other allergic conditions	Weak

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Kanny G 2001 ⁵	Cross-sectional	33110 people up to 60 years. 1129 with food allergy received a second survey	General population	N/A	Food allergy	Self-report survey	Point prevalence (1997 and 1998) Risk factors	The prevalence of food allergy was estimated at 3.24%. The main manifestations were atopic dermatitis for those under 6 years, asthma for those aged 4-6 years and anaphylactic shock for those 30+. Anaphylactic shock was correlated with alcohol and non-steroidal anti-inflammatory drugs and seafood. 97% of anaphylactic shock occurred in adults.2.7% reported anaphylactic shock.		22/818 (2.7%)		Alcohol Medication Pollen		Moderate

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Moneret-Vautrin DA 2001 ⁶	Cross-sectional	100 members of the Allergy Vigilance Network	Clinics of general practitioners, paediatricians, lung specialists and dermatologists	N/A	Anaphylaxis and reactions to foods	Self-report survey	Point prevalence (April 2001 or May 2001)	100 members of the network responded to the questionnaire. 163 serious food allergy incidents were identified. Serious food-allergy related accidents occurred in 46.6% of children under the age of 15 years of age and 53.4% of adults.Anaphylactic shock occurred in 39.9%. The most frequent allergens were peanuts and nuts (27.6%), food cross-reacting with latex (11%) and egg (8.6%).		65/163 (39.9%)		Food		Weak
Mulier S 2006 ⁷	Cross-sectional	156 cases of food allergy	Allergy clinics	1 month to 14 years old, median age 26 months	Clinical features of food allergy	Clinical history Response to elimination diet Labial or oral food challenge	Period prevalence (May 2002 to May 2005)	Anaphylactic shock occurred in 6/156 (3.8%) patients.		6/156 (3.8%)		Food Family history of atopic disease		Weak
Rance F 2005 ⁸	Cross-sectional	2716 out of 3500 children surveyed	150 classes in 8 schools	2.5-14 years, mean 8.9 yrs	Food allergy	Self-report survey	Period prevalence (September 2002)	The point prevalence for food allergy was 4.7%. 4.9% of children had anaphylactic shock as a symptom of food allergy. Cow's milk, eggs and		12/2716 (0.44%)				Moderate

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								peanuts were the main reported causes of anaphylaxis. 182 had true food allergy and prevalence of true food allergy is 12/182=6.593%						
Rymarczk B 2009 ⁹	Cross-sectional	796 adults	Allergy clinics	Mean age 41.5 (SD 13.9 years)	Clinical manifestations of food allergy	Self-report survey	Point prevalence	196/796 (24.6%) patients reported adverse reactions to one or more foods. Anaphylaxis occurred in 146/796 (18.4%) of patients. The most common foods provoking reactions were strawberry (5.0%), cow's milk (3.3%) and tree nuts (3.2%).		36/796 (4.52%)		Food Drugs		Moderate
Vetander M 2011 ¹⁰	Cohort	From 531 records reviewed, 383 children had anaphylaxis of which 371 had reactions to food	Three hospital A&E departments	0-18 years	Anaphylaxis and reactions to foods	Medical records review	Incidence rate (1st January 2007 to 31st December 2007)	32 per 100,000 children for all anaphylaxis, 29 per 100,000 person years (32*0.92 per 100,000 or 128/447739))for food related anaphylaxis. Food was involved in 92% of cases of anaphylaxis. Reactions to peanut and tree nuts were as common as reactions to egg	32 per 100,000 person years OR 143/(447739*1) (0.03%)			Age < 3 years Gender Allergic conditions	Food	Moderate

Causal category of anaphylaxis: Food-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								and milk in the early years. Exposure to airborne allergens increased the risk of anaphylaxis due to food. Pollen allergic children were admitted due to food –related anaphylaxis more during pollen season.						

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Calvani M 2008 ¹¹	Cohort	203 cases of anaphylaxis in children	Hospital	0-17 years, mean 6 years	Anaphylaxis	Hospital databases 2000-2003	Incidence rate (2000 to 2003) Case-fatality rate	203/3,454,208 cases of anaphylaxis in children were identified from hospital records. Anaphylactic shock accounted for 54% of all diagnoses of anaphylaxis and food induced anaphylaxis accounted for 43% of cases. Food induced anaphylaxis was more common in younger children, with an incidence	5.9 (95%CI 5.1 to 6.7) cases per 100,000 resident children OR 1.47 per 100,000 patient years		0.038 cases per 100,000 resident children OR 0.007 per 100,000 patient years	Age Food Shock		Moderate

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								of 12.5 per 100,000 resident children per year in the first year of life, dropping to 6.1 in the first two years and less than 3 per 100,000 resident children per year after the seventh year.						
Capps JA 2010 ¹²	Cross-sectional	816 of 401,152 incidents	General population	All ages, mean not stated	Anaphylaxis	Official records of emergency ambulance callouts	Period prevalence (1st June 2007 to 31st May 2008) Outcome	816 (0.2%) of 401,152 incidents were due to allergic reactions (32/100,000/year). 56% of ambulance callouts for allergic reactions were for first allergic reactions. 22% were children. In adults, females were more likely to be affected whereas in children, genders were equally mixed. No patients died. Foods caused 63% of allergic reactions in children whereas medicines caused 62% in adults. In this study, the term 'allergic reaction callouts' appeared to be used to refer to		816/401152 (0.2%)		Foods Medications	Age Gender Allergic history Seasonal trends Intramuscular adrenaline	Weak

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								potential anaphylaxis.						
Couto M 2011 ¹³	Cross-sectional	1253 individuals	Allergy clinics	15-65 years old	Prevalence of allergic disease	Self-report survey	Point prevalence (16th April 2007 - 27th April 2007)	1253 individuals responded. 3/1253 (0.2%) reported anaphylaxis.		3/1253 (0.2%)				Weak
Gibbison B 2009 ¹⁴	Cohort	81 children and 1269 adults	Critical care units	Not stated	Anaphylaxis admissions to critical care units	Doctor-diagnosed cases over a five year period in national audit data	Cumulative Incidence (2005 to 2009) Risk factors	Anaphylaxis constitutes 0.1% of children's admissions, 0.3% of adult admissions. The number of admissions to critical care units for anaphylaxis is increasing year on year. Critical care units may have an average of one admissions per year for anaphylaxis. 5% of children and adults admitted with anaphylaxis died in hospital.	Incidence rate for 2009 year is 331/95196 (0.3%)		4 children and 60 adults died	Age Gender		High

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Gonzalez-Perez A 2010 ¹⁵	Nested Case-control from asthma cohort	177,00 children and adults with asthma and 200,000 without asthma	People enrolled with GP for at least one year who had at least one contact the previous year	10-79 years	Anaphylaxis from all causes, and in asthma	National database spanning 10 year period	Cumulative incidence (1st January 1996 to 31st December 2005) Risk factors	21.28 per 100,000 person years for no asthma; 50.45 per 100,000 person years for overall asthma. The risk of anaphylaxis was greater in those with serve or non-severe asthma compared with no asthma. Incidence was higher in women (22.65 vs 19.56 for men per 100,000 person years). Other risk factors included atopic dermatitis, antibiotics and lipid lowering drugs.				Asthma Other conditions Food medication s	Gender	Low
Gupta R 2003 ¹⁶	Cohort	49,300 severe allergic conditions in adults and children	Hospital	N/A	Hospital admissions for systemic allergic disorders	National databases of hospital statistics for 11 years	Incidence rate 1990-91 to 2000-01)	There were 13,230 admissions for anaphylaxis over an 11 year period. Relative risk for anaphylaxis was 7.5 (ranging from 6.6 to 8.6) and food-induced anaphylaxis was 5.8 (ranging from 5.1 to 6.8). Anaphylaxis rates rose from 6 to 41 per million admissions						High

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								between 1990-1 and 2000-1.						
Gupta R 2004 ¹⁷	Cohort	N/A	General population	All ages	Allergic disease burden	Secondary analysis of official statistics and databases	Incidence rate (2000 to 2001) Prevalence Outcomes	In 2000, there were 3.8 per 100,000 admissions for anaphylactic shock. The rates differed by gender (3.4 males vs 4.1 females) and age (4.1 for 0-14 years, 3.9 for 15-44 and 3.5 for 45+). 12 deaths were attributed to anaphylaxis in the period 1991-5.	1964/53,000,000 (3.7 per 100,000 population)		1/530,000 person years	Age Gender Social class		High
Helbling A 2004 ¹⁸	Cohort	7739 adult and child patient records reviewed, 226 with anaphylaxis	Allergy clinics	Females 5-74 years, mean 41. Males 8 months-85 years, mean 38 years	Life threatening anaphylaxis with circulatory symptoms	Medical record review Reports from doctors and hospitals	Incidence rate (1 January 1996 to 31 December 1998) Risk factors	Between 8 to 10 people per 100,000 per year suffer life threatening anaphylaxis with circulatory signs. Hymenoptera stings (58.8%), medications (18.1%) and foods (10.1%) were the most common causes. In 5.3% of cases, causes could not be identified.	8.9 (range 7.9 to 9.6) per 100,000 citizens OR 249/27978 (8.9 per 100 years)		3 out of 226 people over a 3 year period, equating to 0.442% per year in the region.	Food Insect venom Medication		Moderate

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Pastorello EA 2001 ¹⁹	Cohort	38,685 children and adults attending A&E, of which 140 had anaphylaxis	Accident and emergency department at one hospital	14-91 years, mean 38.5 years	Anaphylaxis in a general hospital over a two year period	Medical record review	Period prevalence (1997 to 1998) Risk factors	0.4% (1 in 300) had anaphylaxis symptoms. 1 in 3000 of the total population had severe anaphylaxis. Anaphylaxis was mainly linked to foods such as fruit and vegetables and non-steroidal anti-inflammatory drugs. Stings and other causes were less common. Females and atopic patients were more likely to be admitted.		140/38685 (0.4%)		Food Atopy History Age Gender	Age Gender	Low
Quercia O 2012 ²⁰	Cross-sectional	6676 out of 7201 adults returned surveys	General population	Mean 45.6 years	Allergic diseases	Self-report survey	Point prevalence	0.6% of participants had suffered anaphylaxis. There were no significant differences in the prevalence of allergies according to ethnicity.		37/6676 (0.55%)		Ethnicity Conditions		Moderate
Sheikh A 2000 ²¹	Cohort	32.4 million discharges of children and adults	Hospital	N/A	Hospital admissions for acute anaphylaxis	National hospital discharge statistics for 4 years	Study period (1994-95) but for Incidence rate (only 1994 to 95)	The incidence of hospital admissions for acute anaphylaxis increased from 5.6 per 100,000 discharges in 1991-2 to 10.2 in 1994-5. Key causes were medication	10.2 per 100,000 discharges. Incidence rate is 2424/32400000 (0.007%)			Medication Food Venom		High

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								(62%), food (15%) and insect venom (11%).						
Sheikh A 2001 ²²	Cohort	13.5 million emergency inpatient admissions for adults and children, 2323 cases of which with anaphylaxis	Hospital	All ages, mean not stated	Hospital admissions for anaphylaxis	Hospital records database 1991-95	Incidence rate (1991 to 1995)	Rate of anaphylaxis was 17 per 100,000 emergency admissions. Female rate ratio 1.19 (95% CI 1.09-1.29), South England rate ratio 1.35 (1.25-1.47), rural rate ratio 1.35 (1.17-1.59), non deprived area rate ratio 1.32 (1.19-1.44). There were variations in the incidence of inpatient admissions for anaphylaxis by age, gender, geographic area and socioeconomic factors. The risk of anaphylaxis was higher in women of childbearing age and those residing in southern, rural and affluent areas. 12 deaths from anaphylaxis were reported over a 4 year period.	2323/13,500,000 = 17 per 100,000 emergency admissions		12/1350000	Age Gender Deprivation Geographic area		High

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Sheikh A 2008 ²³	Cohort	2.9 million adults and children	People registered with a GP	Not stated	Anaphylaxis	National database derived from 422 general practices, 2001-2005	Incidence rate (2001 to 2005) Lifetime prevalence (2001 to 2005)	Age-sex standardised incidence was 6.7 per 100,000 person years in 2001, rising to 7.9 per 100,000 in 2005. General studies about anaphylaxis continued Lifetime age-sex standardised prevalence of recorded diagnosis of anaphylaxis was 50 per 100,000 in 2001, rising to 75.5 per 100,000 in 2005. By 2005, an estimated 37,800 people in England had experienced anaphylaxis at some point. This equates to 1 in 1333. The rate has been rising over time.	7.9 per 100,000 person-years	37800/50,066,225 (75.5 per 100,000 patients)				High
Tejedor Alonso MA 2011 ²⁴	Cohort	114,626 people admitted to hospital	Hospital	Mean 58 years	Anaphylaxis	Hospital database 1999-2005	Incidence rate (1st January 1998 to 31st December 2005)	Crude cumulative incidence: 1.5 episodes per 5000 admissions. Cumulative incidence adjusted for population: 1.6 episodes per 5000 admissions. Anaphylaxis is rare among hospitalised	34/850,000 [0.2 (95%CI 0.2 to 0.3) per 5000 admission days]	34/114626 (0.03%)			Age Gender Hospital department	High

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								patients. The adjusted cumulative incidence rate of anaphylaxis was 1.6 per 5000 admissions (95% CI 0.8-2.3). Younger people were more likely to experience anaphylaxis, as were those treated in the vascular surgical unit. Men had a lower risk of anaphylaxis than women (hazard ratio 0.5, CI 0.2-0.9).						
Tejedor Alonso MA 2012 ²⁵	Cohort	150,000 adults and children	General population	0-85+	Anaphylaxis	Database review of clinical records for two years	Cumulative incidence (March 2004 - April 2004)	Crude: 103.37 episodes per 100,000 person years. Total standardised rate: 112.2 per 100,000 person years. The incidence of anaphylaxis was highest in 0-4 year olds (313.58 per 100,000 person years). For those over 10 years, there was a trend towards a higher incidence in females, but this did not reach statistical significance. Food and	336/325046 (103.37 per 100,000 patients)			Food Medication Latex Exercise	Age Gender	High

Causal category of anaphylaxis: General														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
								medications were key causes.						
Worm M 2012 ²⁶	Cohort	2012 adults and children, included from 2633	83 allergy clinics	1-87 years	Anaphylaxis	Registry survey of allergy centres	Risk factors (2006-2010)	The most common causes of anaphylaxis were insect venom (50%), food (24%) and medication (17%). Skin was the most commonly affected *84%), followed by cardiovascular (72%) and respiratory symptoms (68%). Older patients were more likely to suffer respiratory symptoms. 53% had one or more concomitant diseases.				Gender Age Other conditions		High

Causal category of anaphylaxis: Latex-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Draisci G 2011 ²⁷	Cohort	294 women scheduled for caesarean section and 294 women undergoing gynaecological surgery	Hospital	Mean 33 years	Latex sensitisation	Self-report survey Blood test Skin-prick test	Cumulative incidence (July 2003 to September 2008)	15 tested positive in pregnant women and 5 non-pregnant women for latex sensitisation.. 2/10=10% experienced anaphylaxis given they were positive for latex sensitisation. There was a higher rate of latex sensitisation and anaphylaxis in pregnant women undergoing caesarean section compared to non-pregnant women undergoing surgery.	2/588 (0.34%)			Allergy history Number of operations Age Weight		Low

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Ayala F 2006 ²⁸	Cross-sectional	649 people hospitalised in the dermatology department for suspected adverse drug reactions	Hospital	N/A	Adverse drug reactions in dermatology patients	Clinical examination Biopsy if needed	Period prevalence (January 2001 to May 2002) Outcomes	Of those admitted with suspected adverse drug reactions, 2.5% had anaphylactic shock. There was no statistically significant relationship between gender and the type of adverse reaction.		16/649 (2.5%)				Weak
Borch JE 2006 ²⁹	Cross-sectional case control	96 out of 3642 adults and children, 13 of whom completed all investigations	Hospital	2-99 years, mean 61 years	Penicillin allergy	Self-report survey Challenge test Skin prick test	Period prevalence (2003)	In people with penicillin allergy, 14/96 (14.5%) had experienced immediate reactions such as anaphylaxis, hives or vomiting. 10/14 (71.4%) of these experienced anaphylaxis.		3/96 (3.1%)		Medication Family history		Moderate
Bousquet PJ 2007 ³⁰	Cohort study part of very large case and control cohort	210 out of 973 patients tested	Hospital	Mean 32.9 years	B-lactam hypersensitivity reactions	Provocation test Skin prick test Self-report survey over 8 year period	Period prevalence (1996 to 2004)	Anaphylaxis usually occurred in the first hour after drug administration. Later reactions included hives and maculopapular exanthema. 19.1% had anaphylaxis without shock and 17.6% had anaphylactic shock		40/973 (4.1%)				Moderate

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Branellec A 2008 ³¹	Cross-sectional	1057 patients	General practice clinics	All ages, mean not stated	Prevalence of penicillin allergy	Self-report survey	Period prevalence (March 2005)	1057 patients participated, 11 reported anaphylactic shock.		11/1057 (1.04%)				Weak
Dietrich W 2007 ³²	Cross-sectional	12,403 adults and children undergoing cardiac surgery with aprotinin	Hospital	Mean 3.5 years (SD 5.4 years) for children, mean 63.5 (SD 16.9) years for adults	Anaphylactic reactions to aprotinin	Hospital database completed by doctors	Period prevalence (1995 to 2003)	93% of cardiac operations were performed using aprotinin. The overall rate of hypersensitivity reactions / anaphylaxis was low (0.19%)		23/12403 (0.2%)	1/12403= 8 per 100,000 person per year			Strong
Hopf Y 2008 ³³	Cohort	1101 adults with emergency admission over a two week period	Hospital	Not stated	Adverse drug reaction related admissions	Screening of admissions data by pharmacists and researchers	Cumulative Incidence (22nd May 2006 to 5th June 2006)	The prevalence of adverse drug reaction admissions was 2.7% (ranging from 1.8-3.7). Of these, anaphylaxis was noted as a symptom in only one case.	1/1101 (0.09%)					Low
Lange L 2008 ³⁴	Cross-sectional	1446 children out of 1447	Tertiary hospital	0-211 months. Median 43 months	Allergic drug reactions	Self-report survey	Period prevalence (May 2004 to November 2004)	The reported lifetime prevalence of adverse drug reactions in children was 7.5%. 3 out of 1446 children (0.2%) had experienced an anaphylactic reaction.		3/1446 (0.2%)		Allergy history Medication type Age		Moderate

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Laporte J-R 2003 ³⁵	Case-control	184 cases and 1003 controls	Hospital	Median 52 years	Anaphylactic reactions to various medications in hospital	Review of hospital records	Incidence rate (1992 to 1997)	For most analgesics and antibiotics, incidence ranged between 5 and 15 cases per 100,000 exposed patients. There was wide variation in the incidence of anaphylaxis among different medications. For instance the rate per 100,000 exposed cases was 2.1 for aspirin, 32 for parenteral penicillin and 378 for parenteral plasma. There is a relatively low risk for dipyrone, diclofenac, paracetamol, ampicillin, cloxacillin and cephalosporins. Parenteral penicillin, dextran, contrast media. Blood and pentoxifylline have an intermediate risk. The highest incidence was observed in those receiving plasma and streptokinase.				Medication		Moderate

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Laxenaire MC 2001 ³⁶	Cohort	467 children and adults suffering anaphylaxis during anaesthesia	Hospital allergy centres	1-90 years	Anaphylaxis during anaesthesia	Self-report survey Clinical history Skin-prick test Blood test	Risk factors (2 years)	467 patients known to suffer from anaphylaxis. Women were more likely to suffer anaphylaxis during anaesthesia than men, relative to the overall number of operations for each gender. The most common causes were neuromuscular blocking drugs (69.2%), followed by latex (12%) and antibiotics (8%). Atopy was present in 25% of cases, asthma in 9% and food allergy in 3%.				Age Gender Medication Food atopy		Moderate
Lynch RM 2004 ³⁷	Case-control		Emergency department	15 - 91 years old	Incidence of anaphylaxis in patients receiving N-acetylcysteine	Clinical examination	Cumulative incidence (January 1997 to June 1999)	64 patients received N-acetylcysteine infusions; 31 (48.4%) developed an anaphylactoid reaction. 19 patients who reacted were commenced on N-acetylcysteine prior to receipt of paracetamol concentrations and 15 (48.4%) were categorised as high-risk.						Moderate

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Mertes PM 2003 ³⁸	Cohort	789 adults and children	40 allergy centres	Not stated	Anaphylaxis during anaesthesia	Clinical history Self-report survey Skin-prick test Blood test	Risk factors (1 Januar 1999- 31 December 2000)	Women were more likely than men to experience anaphylaxis during anaesthesia. The most common causes were neuromuscular blocking agents, latex and antibiotics.				Medication Latex Atopy Gender		Low
Mertes PM 2011 ³⁹	Cohort	2516 adults and children	General population	Not stated	Anaphylaxis during anaesthesia	National databases over an 8-year period	Cumulative incidence (1st January 1997 to 31st December 2004) Risk factors	100.6 per million estimated annual incidence of IgE mediated allergic reactions during anaesthesia. The median annual incidence of anaphylaxis during anaesthesia was higher for adult women but not for female compared to male children. The most common causes were neuromuscular blocking agents (58%), latex (20%) and antibiotics (13%). Female hormones may also play a role.	100.6 (95%CI 76.2 to 125.3)per million procedures			Medication Latex	Gender	Moderate

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Michalska-Krzanowska G 2006 ⁴⁰	Cohort	3560 patients who received anaesthesia	Hospital	N/A	Anaphylaxis due to anaesthetic agents	Medical record review	Cumulative incidence	Symptoms of anaphylaxis were recorded in 130 anaesthetic procedures. Although cisatracurium was the most common neuromuscular blocking agent (NMBA), the symptoms of anaphylaxis were observed only in patients treated with suxamethonium, pancuornium or rocursionium.	130/3560 (3.6%)			NMBA		Moderate
Nybo M 2008 ⁴¹	Systematic review	25 studies with people undergoing cardiac surgery, total population not stated; only 2 studies met our inclusion criteria (Laxenaire MC 2001 and Mertes PM 2003)	Hospital	N/A	Anaphylactic reactions to protamine sulphate during cardiac surgery	N/A	Cumulative incidence	The incidence of anaphylactic reactions to protamine sulphate was 0.69% in 16 prospective studies and 0.19% in 9 retrospective studies. There was a low incidence of anaphylactic reactions to protamine sulphate during cardiac surgery, but studies included in the review tended to be of low quality.	8/1165 (0.69%) prospective 34/17573 (0.19%) retrospective					Low

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Pakravan N 2008 ⁴²	Cohort	169 out of 193 people with acetaminophen overdose. 22 underwent more detailed study	Hospital	Mean 37 years	Anaphylactoid reactions to N-acetylcysteine	Records review Blood tests Other clinical tests	Risk factors	The most common reactions to intravenous N-acetylcysteine in people with acetaminophen overdose were nausea and vomiting, flushing and pruritus. Factors associated with moderate to severe adverse effects included female gender and family history of allergy.				Age Gender Dosage Drug allergy Family history		Low
Quiralte J 2007 ⁴³	Cohort	174 out of 223 adults and children tested 49 referred due to history of anaphylaxis	Hospital records of NSAID-sensitive patients (NSAID = Nonsteroidal anti-inflammatory drug)	5-78 years, mean 32.2 years	NSAID reactions	Single blind placebo controlled oral challenge	Cumulative incidence Outcomes	16% of NSAID reactions involved anaphylaxis. In people reacting to NSAIDs, those experiencing anaphylaxis were more likely to be women.	50/317 (16%)			Atopy Conditions Gender		Low

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/ type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Rasmusse n TA 2012 ⁴⁴	Cohort	2,300,227 children	General populati on	0-18 years	Outcomes from vaccination	National databases	Incidence rate (1st January 1980 to 31st December 2009) Outcomes	Anaphylactic shock: 1.45 per 100,000 person years (95% CI 1.32 to 1.59). The incidence of anaphylactic shock following vaccination was higher for males. Incidence was predicted to be higher in the third quarter of the year.	1.45 per 100,000 person years (95%CI 1.32 to 1.59)			Age Gender	Season	High
Sandiland s EA 2009 ⁴⁵	Systema tic review	People given acetylcyst eine	Hospital	N/A	Adverse reactions from acetylcystein e	Varied between studies included in the review	Risk factors Outcomes	Anaphylactoid reactions have been reported in 23% to 48% of patients receiving acetylcysteine. Nausea and vomiting are the most common manifestations. There have been few fatalities. Atopy is a risk factor Only 3 studies included in this systematic review met our inclusion criteria. These studies were Waring WS 2008, Pakravan N 2008 and Lynch RM 2004.				Atopy		Moderate

Causal category of anaphylaxis: Medication-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
van Puijenbroek EP 2002 ⁴⁶	Case-control	190 cases and 26,720 controls, comprising adults and children	General population reporting adverse drug reactions	All aged 10 years or more, mean 52.2 (SD 17.6) years	NSAID induced anaphylaxis	Drug reaction reports to pharmacovigilance system	Risk factors (January 1985-2000)	The risk of reporting an anaphylactic reaction may be greater with NSAIDs than for other drugs (adjusted reporting odds ratio 9.4, 95% CI 6.9-12.7).				Age Gender Medication type		Moderate
Waring WS 2008 ⁴⁷	Cohort	362 out of 1091 adults presenting to hospital after acute acetaminophen	Hospital	Median 35 years	Anaphylactoid reactions to N-acetylcysteine	Data collected by staff specifically for study	Cumulative incidence (March 2005 to June 2006)	14.9% of patients given N-acetylcysteine suffered anaphylactoid reactions. Anaphylactoid reactions were less common in people with high serum acetaminophen concentrations, suggesting some type of protective effect.	54/362 (14.9%)			Acetaminophen concentrations		High

Causal category of anaphylaxis: Stinging insect-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Celikel S 2006 ⁴⁸	Cross-sectional	494 out of 1245 surveys returned from adults	Beekeepers	Mean 48.22 (SD 11.47)	Systemic reactions to bees and bee products in beekeepers	Self-report survey	Period prevalence (December 2004 to June 2005) Risk factors	6.5% of beekeepers had a systemic reaction to bee sting in the past 12 months. 2% of these reactions involved anaphylaxis. The risk of systemic reactions increased when atopic disease was present.		9/494 (1.82%)		Age Duration of beekeeping Atopy		Weak

Causal category of anaphylaxis: Venom-induced														
Reference	Study design	Study population		Age (range, mean)	Outcomes			Main findings	Frequency of occurrence (original)			Risk/prognostic factors studied		Overall Quality
		Number/type	Source		Outcome(s) studied	Method of assessment	Measure focus		Incidence	Prevalence	Case-fatality rate	Risk factors	Prognostic factors	
Perez Pimiento AJ 2007 ⁴⁹	Cohort	115 children and adults who had anaphylactic reaction to wasp sting	General population	10-80 years, mean 40.2 (SD 15.9) years	Anaphylactic reaction to wasp sting	IgE tests	Risk factors Outcomes	In people suffering anaphylaxis after a wasp sting, the most common symptoms involved the skin (90%), respiratory (55%), cardiovascular (34%) and gastrointestinal areas (22%). Age, gender and atopy were not related to the severity of the reaction.				Atopy Age Gender	Atopy Age Gender	Low

Table E2: Quality scoring of studies

Study design: Systematic reviews										
Reference	Quality domains									
	Focused question	Inclusion of appropriate studies	Inclusion of eligible studies	Quality assessment of studies	Appropriateness of synthesis	Overall results of review	Applicability to local populations	Considering all relevant outcomes	Benefits vs. harms/costs	Overall quality assessment
Nybo M 2008 ⁴¹	✓	✓	✓	X	✓	✓	✓	✓	X	Low
Sandilands EA 2009 ⁴⁵	✓	✓	✓	✓	✓	✓	✓	✓	X	Moderate

Study design: Cohort														
Reference	Quality domains													
	Q1	Q2	Q3	Q4	Q5	Q6	Q7a	Q7b	Q8	Q9	Q10	Q11	Q12	Overall quality
Calvani M 2008 ¹¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Draisci G 2011 ²⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	X	Low
Gibbison B 2009 ¹⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Gupta R 2003 ¹⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Gupta R 2004 ¹⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Helbling A 2004 ¹⁸	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Hopf Y 2008 ³³	✓	✓	✓	✓	✓	✓	X	X	✓	?	✓	✓	✓	Low
Laxenaire MC 2001 ³⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate

Study design: Cohort														
Reference	Quality domains													
	Q1	Q2	Q3	Q4	Q5	Q6	Q7a	Q7b	Q8	Q9	Q10	Q11	Q12	Overall quality
Lynch RM 2004 ³⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Mertes PM 2003 ³⁸	✓	✓	✓	✓	✓	✓	X	X	✓	?	✓	✓	✓	Low
Mertes PM 2011 ³⁹	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Michalska-Krzanowska G 2006 ⁴⁰	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Pakravan N 2008 ⁴²	✓	✓	✓	✓	✓	✓	X	X	✓	✓	✓	✓	✓	Low
Pastorello EA 2001 ¹⁹	✓	✓	✓	✓	✓	✓	X	X	✓	?	✓	✓	✓	Low
Perez Pimiento AJ 2007 ⁴⁹	✓	✓	✓	✓	✓	✓	X	X	✓	?	✓	✓	✓	Low
Quirarte J 2007 ⁴³	✓	✓	✓	✓	✓	✓	X	X	✓	?	✓	✓	✓	Low
Rasmussen TA 2012 ⁴⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Sheikh A 2000 ²¹	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Sheikh A 2001 ²²	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Sheikh A 2008 ²³	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Tejedor Alonso MA 2011 ²⁵	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Tejedor Alonso MA 2012 ²⁴	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High

Study design: Cohort														
Reference	Quality domains													
	Q1	Q2	Q3	Q4	Q5	Q6	Q7a	Q7b	Q8	Q9	Q10	Q11	Q12	Overall quality
Vetander M 2011 ¹⁰	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	Moderate
Waring WS 2008 ⁴⁷	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High
Worm M 2012 ²⁶	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	High

Study design: Cross-sectional										
Reference	Quality domains									
	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and methods	Intervention integrity	Analyses	Overall quality	
Alvarado MI 2006-1	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	
Asero R 2009 ²	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	
Ayala F 2006 ²⁸	Moderate	Moderate	Weak	Weak	Strong	Moderate	N/A	Moderate	Weak	
Borch JE 2006 ²⁹	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	N/A	Moderate	Moderate	
Bousquet PJ 2007 ³⁰	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	N/A	Strong	Moderate	
Branellec A 2008	Weak	Weak	Weak	Strong	Moderate	Moderate	N/A	Moderate	Weak	
Calvani M 2011 ³	Moderate	Weak	Moderate	Moderate	Moderate	Moderate	N/A	Moderate	Moderate	
Capps JA 2010 ¹²	Moderate	Moderate	Weak	Weak	Strong	Moderate	N/A	Moderate	Weak	
Celikel S 2006 ⁴⁸	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak	

Study design: Cross-sectional									
Reference	Quality domains								
	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and methods	Intervention integrity	Analyses	Overall quality
Couto M 2011 ¹³	Moderate	Moderate	Weak	Weak	Moderate	Weak	N/A	Moderate	Weak
Derby CJ 2005 ⁴	Weak	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak
Dietrich W 2007 ³²	Strong	Strong	Strong	Strong	Moderate	Strong	N/A	Strong	Strong
Kanny G 2001 ⁵	Strong	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate
Lange L 2008 ³⁴	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	N/A	Moderate	Moderate
Moneret-Vautrin DA 2001 ⁶	Moderate	Moderate	Weak	Weak	Moderate	Weak	N/A	Moderate	Weak
Mulier S 2006 ⁷	Moderate	Moderate	Weak	Weak	Moderate	Moderate	N/A	Moderate	Weak
Quercia O 2012 ²⁰	Strong	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate
Rance F 2005 ⁸	Strong	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate
Rymarczk B 2009 ⁹	Moderate	Moderate	Moderate	Weak	Moderate	Moderate	N/A	Strong	Moderate

Study design: Case-control													
Reference	Quality domains												
	Q1	Q2	Q3	Q4	Q5	Q6a	Q6b	Q7	Q8	Q9	Q10	Q11	Overall quality
Gonzalez-Perez A 2010 ¹⁵	X	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	Low
Laporte J-R 2003 ³⁵	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	Moderate
van Puijenbroek EP 2002 ⁴⁶	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	Moderate

Box E5: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8 Reg number not available at present
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1

Section/topic	#	Checklist item	Reported on page #
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

Appendix 1: Reasons for excluding studies

Pre-year 2000 or post year 2012 (n = 20)

1. Theissen JL, Zahn P, Theissen U, Brehler R. [allergic and pseudo-allergic reactions in anesthesia. I: Pathogenesis, risk factors, substances]. *Anesthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie* 1995;30(1):3-12.
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14. Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M. Latex allergy: Clinical features and cross-reactivity with fruits. *Annals of Allergy* 1994;73(4):309-14.
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16. Dietrich W, Spath P, Ebell A, Richter JA. Prevalence of anaphylactic reactions to aprotinin: Analysis of two hundred forty-eight reexposures to aprotinin in heart operations. *Journal of Thoracic and Cardiovascular Surgery* 1997;113(1):194-201.
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Outside Europe (n = 86)

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Study design unable to yield chosen outcomes (n = 14)

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