

ORIGINAL ARTICLE

ANAPHYLAXIS

# Symptom profile and risk factors of anaphylaxis in Central Europe

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## Keywords

Allergy; anaphylaxis; elicitors; symptoms; risk factors.

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## Abstract

**Background:** Anaphylaxis is the most severe manifestation of an IgE-dependent allergy. Standardized acquired clinical data from large cohorts of well-defined cases are not available. The aim of this study was to analyse the symptom profile and risk factors of anaphylaxis in a large Central European cohort.

**Methods:** We acquired data from patients in Germany, Austria and Switzerland who experienced a severe allergic reaction defined by the onset of severe pulmonary and/or severe cardiovascular symptoms. The data were gained via an online questionnaire from 83 medical centres specialized in allergy. Data were collected from 2006 to 2010 and analysed by using a multinomial regression model.

**Results:** A total of 2012 paediatric and adult patients were included into the present analysis. The skin (84%) was the most frequently affected organ followed by the cardiovascular (72%) and the respiratory (68%) system. The regression model analysing the onset of cardiovascular versus respiratory symptoms revealed a strong impact of age (adjusted OR = 6.08; 95% CI, 3.35–11.01;  $P < 0.001$ ). Furthermore, the elicitor food (adjusted OR = 0.29; 95% CI, 0.21–0.41,  $P < 0.001$ ) and the presence of atopic diseases (adjusted OR = 0.54; 95% CI, 0.40–0.73,  $P < 0.001$ ) were significantly associated with the onset of respiratory symptoms.

**Conclusion:** Data from individuals who experienced anaphylaxis can support the identification of risk factors. The present study indicates that age, the elicitor itself and the presence of atopic diseases have an impact on the symptom profile of anaphylaxis. Identifying further risk factors of anaphylaxis is of significant importance for clinical practice in the future.

Anaphylaxis is defined as a serious hypersensitivity reaction that is rapid in onset and may cause death (1, 2). The incidence rate of anaphylaxis varies from 7.9 to 49.8 per 10 000 person-years depending on the region, but more importantly on the

definition and inclusion criteria applied (3–5). The literature citing the causes of anaphylaxis indicates that drugs, insect venom and food are the most frequent triggers (6, 7). Anaphylaxis can present with various clinical symptoms involving different organ systems including the skin, gastrointestinal and respiratory tract and the cardiovascular system. The involvement of the skin is most frequent and has been documented in 80–90% of reported episodes (8, 9). The respiratory tract is affected in up to 70% of patients, and the cardiovascular system and the gastrointestinal tract have been reported to be less

## Abbreviations

aOR(s) adjusted odds ratio(s); CI confidence interval; CVD cardiovascular diseases; ENT ear, nose and throat; IgE immunoglobulin E; SD standard deviation.

frequently involved (7, 8). The skin affection may help to differentiate anaphylaxis from other clinical conditions such as myocardial infarction or panic attack (10). However, in 10–20% of the patients, skin symptoms are absent or not recognized (8). In such cases, the correct diagnosis of anaphylaxis may be missed. The respiratory and/or cardiovascular symptoms are most frequently associated with life-threatening situations and anaphylactic fatalities (11).

The anaphylaxis registry ([www.ANAPHYLAXIE.net](http://www.ANAPHYLAXIE.net)) was initiated to obtain detailed clinical data from allergists treating patients with anaphylaxis in German-speaking countries. The objective of this study was to investigate whether the symptom profile of anaphylaxis is determined by specific risk factors.

## Methods

### The anaphylaxis registry

The anaphylaxis registry acquires data from patients with a history of a severe allergic reaction since July 2006. Data are delivered by medical centres specialized in allergy. The submission of the pseudonymized data is realized via a password-protected standardized online questionnaire. The registry fulfils local data protection policies. Approval by the ethics committee of the Charité-Universitätsmedizin Berlin was obtained.

### The centres of the registry

The centres were selected based on their allergy expertise. The participation in the registry is voluntary. As of November 2010, a total of 79 clinics and four private practices from Germany ( $n = 67$ ), Austria ( $n = 8$ ) and Switzerland ( $n = 8$ ) were associated with the registry. They represent 37 dermatology, two ear, nose and throat (ENT), four pulmonary and 40 paediatric centres, all specialized in allergy. More than 50% of the centres are university related.

### The questionnaire

Data in eight categories are collected: socio-demographics, clinical symptoms, elicitors, allergy history, diagnostic tests, presence of additional factors during the reaction, therapeutic and preventive measures.

If the elicitor of the reaction is known, it is stated as 'confirmed' or 'suspected' by the attending physician. The judgement results from medical history of the patient and/or the diagnostic measures performed. The results of diagnostic measures to confirm the cause of the reaction, such as skin tests, determination of specific immunoglobulin E (IgE) antibodies (free choice of the type of test) and challenge-tests, are recorded if positive.

### Registry inclusion and exclusion criteria, data management

To qualify for inclusion in the registry, the reactions must be severe and systemic, as defined by at least one severe pulmo-

nary (dyspnoea, stridor, apnoea) and/or one severe cardiovascular symptom (decreased alertness, tachycardia, decrease of blood pressure, loss of consciousness, collapse, cardiac arrest). Only reactions that had occurred less than 12 months ago before the first visit date in the centre shall be reported to minimize the recall bias. Reactions are entered into the system by medical staff after the diagnostic procedure has been completed and diagnosis confirmed. The data are regularly monitored by qualified research staff and examined for plausibility and the presence of inclusion/exclusion criteria on a single-case basis. By November 2010, data from 2633 anaphylactic reactions had been registered.

### Study population

To be eligible, reactions must have occurred between January 2006 and October 2010. If concomitant allergic symptoms were missing and a reaction occurred with severe cardiovascular symptoms only, the elicitor of the anaphylactic reaction was required to be stated as 'confirmed' by the attending physician to be eligible. If concomitant allergic symptoms were missing and only pulmonary symptoms were reported, the reaction was excluded. Furthermore, reactions with cutaneous and/or gastrointestinal symptoms only were excluded as well. Finally, those reactions occurring during a provocation test were not included as they form part of a diagnostic procedure. Patients with mastocytosis and increased tryptase levels were excluded from this analysis owing to a possible interference with the severity of symptoms (12).

### Study variables

The following data set from the questionnaire was analysed in this study: gender, age, date of the reaction, clinical symptoms, elicitors of the reaction and concomitant diseases.

### Statistical analysis

Data management and descriptive analysis were performed with SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Multinomial logistic regression was performed using STATA version 11 (StataCorp, LP, Lakeway Drive, TX, USA).

Data were summarized: for continuous data (e.g. age), mean  $\pm$  SD, median and range were determined; for categorical data, absolute and relative frequency was calculated.

A multinomial regression model was used to analyse whether the mode of the development of anaphylactic life-threatening symptoms is influenced by certain factors. The multinomial regression describes the interrelationship of defined clinical phenotypes (only respiratory; only circulatory; respiratory and circulatory symptoms) with independent variables, that is, age, gender, elicitors of anaphylaxis and concomitant diseases. The output of the multinomial logistic regression is presented as a set of three dichotomous logistic regressions that provide a pairwise comparison of the phenotypes as follows: only respiratory versus only circulatory symptoms; only respiratory ver-

sus respiratory and circulatory symptoms; and only circulatory versus respiratory and circulatory. Results are reported as adjusted odds ratio with 95% confidence intervals (CI), that is, all independent variables were included simultaneously in the models. *P*-values below 0.05 were considered to be significant. Reported *P*-values were descriptive, and no adjustments were made for multiple testing.

#### Arrangement of the population for the regression model

For the regression model, the cohort was divided into six age groups: 0–9 years (children), 10–17 years (adolescents), 18–30 years (young adults), 31–50 years (adults), 51–65 years (young seniors) and older than 65 years (seniors). The youngest group (0–9 years) served as reference category in the regression model. Females were the reference category in the regression model investigating sex as a risk factor.

The elicitors were grouped into 'insects', 'food', 'drugs', 'others' and 'unknown'. As food, drugs and insects were the main elicitors of anaphylaxis, all other registered elicitors such as latex were categorized as 'others'. The elicitor 'insects' served as reference category in the regression model as insects were the most common elicitors of anaphylaxis.

Concomitant diseases were categorized into 'cardiovascular diseases (CVD) no atopy', 'atopy no CVD', 'CVD + atopy', 'other' and 'none'. The group 'CVD no atopy' covered patients who had CVD but no atopy. The group 'atopy no CVD' included patients who had atopy but no CVD. The group 'CVD + atopy' covered patients who had CVD and atopy. The group 'other' included patients who had concomitant diseases other than CVD and atopy. The group 'none' was comprised of patients with no concomitant disease. This group served as the reference category for the regression model.

#### Results

At data analysis (November 2010), 2633 anaphylactic reactions were recorded. Of them, 320 reactions occurred before January 2006 and were excluded; 210 reactions were excluded because of insufficient symptom severity; and 91 patients with mastocytosis and increased tryptase levels were also excluded, resulting in 2012 anaphylactic reactions for analysis (Fig. 1). Fifty-eight centres (28 paediatric, 27 dermatologic, two pulmonary and one ENT) provided data for the present analysis, which included five centres from Austria, six centres from Switzerland and 47 centres from Germany. 1985 patients experienced a total of 2012 reactions; 940 (47%) were men. The age of eligible patients ranged from 2 months to 87 years (mean  $\pm$  SD, 39.6  $\pm$  21.2; median, 42.5).

#### The skin is the most frequently affected organ system

The skin was the most common affected organ system in our cohort (84%), followed by symptoms of the cardiovascular (72%) and the respiratory system (68%). The gastrointestinal tract was involved in 40% of the reactions (Table 1).

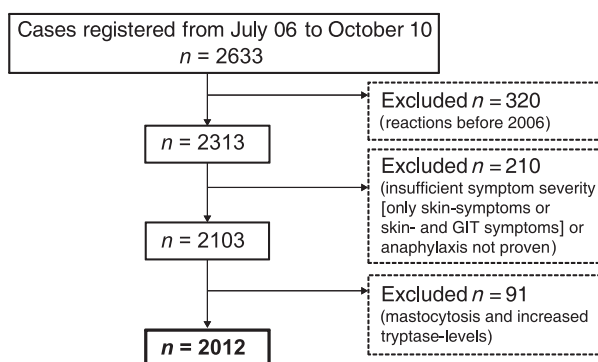


**Figure 1** Flow chart of the study population.

#### Venom is a frequent confirmed elicitor of anaphylaxis

In 1904 (95%) reactions, the elicitor of the anaphylactic reaction was known. The most common elicitors in this cohort were insect stings (50%), followed by food (24%) and drugs (17%). Three per cent of the reactions were caused by other elicitors (Table 2). The elicitor was stated as 'confirmed' in

**Table 1** Frequency of symptoms of registered anaphylactic reactions (8836 registered symptoms in 2012 reactions)

| Symptoms                | n (%)       |
|-------------------------|-------------|
| <b>Cutaneous</b>        | 1690 (83.9) |
| Urticaria               | 985 (49.0)  |
| Angioedema              | 932 (46.3)  |
| Pruritus                | 728 (36.2)  |
| Flushing                | 375 (18.6)  |
| Erythema                | 243 (12.1)  |
| <b>Cardiovascular</b>   | 1442 (71.7) |
| Dizziness               | 729 (36.2)  |
| Drop in blood pressure  | 434 (21.6)  |
| Collapse                | 421 (20.9)  |
| Tachycardia             | 297 (14.8)  |
| Decreased alertness     | 305 (15.2)  |
| Loss of consciousness   | 276 (13.7)  |
| Shivering               | 53 (2.6)    |
| Cardiac arrest          | 38 (1.9)    |
| Sweating                | 36 (1.8)    |
| Fatigue                 | 12 (0.6)    |
| <b>Respiratory</b>      | 1359 (67.5) |
| Dyspnoea                | 1252 (62.2) |
| Stridor                 | 201 (10.0)  |
| Cough                   | 44 (2.2)    |
| Apnoea                  | 30 (1.5)    |
| Chest tightness         | 17 (0.8)    |
| <b>Gastrointestinal</b> | 797 (39.6)  |
| Nausea                  | 467 (23.2)  |
| Vomiting                | 271 (13.5)  |
| Dysphagia               | 129 (6.4)   |
| Diarrhoea               | 122 (6.1)   |
| Abdominal pain          | 122 (6.1)   |
| Incontinence            | 53 (2.6)    |
| Other symptoms          | 150 (7.5)   |

**Table 2** Elicitors of anaphylactic reactions ( $n = 2012$ ; in  $n = 108$  (5%), the elicitor was unknown)

| Elicitors             | $n$ (%)     | $n$ (%)   |           |
|-----------------------|-------------|-----------|-----------|
|                       |             | Confirmed | Suspected |
| <b>Insects</b>        | 1014 (50.4) | 944 (93)  | 70 (7)    |
| Yellow jacket         | 705 (69.5)  | 655 (93)  | 50 (7)    |
| Bee                   | 176 (17.4)  | 166 (94)  | 10 (6)    |
| Hornet                | 56 (5.5)    | 54 (96)   | 2 (4)     |
| Bumble bee            | 4 (0.4)     | 4 (100)   | 0 (0)     |
| Horse fly             | 2 (0.2)     | 2 (100)   | 0 (0)     |
| Mosquito              | 2 (0.2)     | 1 (50)    | 1 (50)    |
| <i>Insects*</i>       | 69 (6.8)    | 62 (90)   | 7 (10)    |
| <b>Food</b>           | 488 (24.3)  | 341 (70)  | 147 (30)  |
| Peanuts and legumes   | 105 (21.5)  | 91 (87)   | 14 (13)   |
| Animal-derived food†  | 99 (20.3)   | 79 (80)   | 20 (20)   |
| Treenuts              | 96 (19.7)   | 70 (73)   | 26 (27)   |
| Cereals               | 43 (8.8)    | 27 (63)   | 16 (37)   |
| Vegetables            | 38 (7.8)    | 22 (58)   | 16 (42)   |
| Fruits                | 36 (7.4)    | 26 (72)   | 10 (28)   |
| Spices and others     | 30 (6.1)    | 16 (53)   | 14 (47)   |
| Others                | 10 (2.0)    | 6 (60)    | 4 (40)    |
| Additives             | 8 (1.6)     | 4 (50)    | 4 (50)    |
| <i>Food*</i>          | 23 (4.7)    | 0 (0)     | 23 (100)  |
| <b>Drugs</b>          | 336 (16.7)  | 197 (59)  | 139 (41)  |
| Analgesics            | 149 (44.3)  | 81 (54)   | 68 (46)   |
| Antibiotics           | 68 (20.2)   | 49 (72)   | 19 (28)   |
| Local anaesthetics    | 43 (12.8)   | 15 (35)   | 28 (65)   |
| Others                | 19 (5.7)    | 13 (68)   | 6 (72)    |
| X-ray contrast media  | 18 (5.4)    | 11 (61)   | 7 (39)    |
| Muscle relaxants      | 13 (3.9)    | 11 (85)   | 2 (15)    |
| Proton pump inhibitor | 13 (3.9)    | 10 (77)   | 3 (23)    |
| Steroids              | 5 (1.5)     | 3 (60)    | 2 (40)    |
| Volume replacement    | 4 (1.2)     | 3 (75)    | 1 (25)    |
| Narcotics             | 4 (1.2)     | 1 (25)    | 3 (75)    |
| Others                | 66 (3.3)    | 51 (77)   | 15 (23)   |

\*The elicitor was not given in more detail.

†Including cow's milk, hen's egg, fish, meat, shellfish.

80% ( $n = 1533$ ) of the reactions, and for the remaining cases, it was stated as 'suspected' based on the judgement of the attending physician after diagnostic tests were performed and diagnosis was confirmed. Elicitors in the insect group were most frequently confirmed (93%) followed by food (70%) and drugs (59%) (Table 2).

A history of one or more concomitant diseases was registered in 1055 (53%) patients. Atopic diseases (32%) such as atopic dermatitis (8%), allergic asthma (15%) and allergic rhinoconjunctivitis (22%) were common, followed by CVD (19%). Thyroid diseases (6%) were the third most common disease group. Malignant, metabolic and other diseases were reported in <5% of the patients (Table 3).

### Risk factor analysis

To perform a risk analysis, we defined three groups based on their clinical reaction patterns (Table 4). Adjusted odds ratios (aORs) of three dichotomous comparisons of the clinical

**Table 3** Frequency of concomitant diseases in the anaphylaxis cohort. A total of 1343 concomitant diseases were reported in 1055 patients (= 53% of all 1985 registered patients)

| Concomitant diseases         | $n$ (%)    |
|------------------------------|------------|
| Atopy                        | 632 (31.8) |
| Atopic dermatitis            | 166 (8.4)  |
| Allergic asthma              | 291 (14.7) |
| Allergic rhinoconjunctivitis | 429 (21.6) |
| Cardiovascular diseases      | 368 (18.5) |
| Thyroid diseases             | 126 (6.3)  |
| Other allergies              | 52 (2.6)   |
| Malignant diseases           | 40 (2.0)   |
| Metabolic diseases           | 39 (2.0)   |
| Others                       | 28 (1.4)   |
| Urticaria                    | 23 (1.2)   |
| Gastrointestinal diseases    | 13 (0.7)   |
| Skin disease                 | 13 (0.7)   |
| Rheumatism                   | 5 (0.3)    |
| Neurological diseases        | 4 (0.2)    |

reaction patterns of anaphylaxis were calculated by multinomial regression analysis.

The analysis identified independent variables as risk factors for the manifestation of only circulatory versus only respiratory symptoms (Fig. 2A). Age was identified as the risk factor for the onset of circulatory symptoms by high aORs in older patients. If children served as the reference category, adolescents displayed an aOR of 1.45 (95% CI, 0.81–2.59;  $P = 0.215$ ), followed by a further increase in young adults (aOR = 4.47; 95% CI, 2.58–7.75;  $P < 0.001$ ). The increasing aORs persisted, reaching 6.08 (95% CI, 3.35–11.01;  $P < 0.001$ ) in seniors.

A decreased risk (reflected by an OR < 1) was detected for all elicitors if the reference category was insects. Food and drugs displayed an aOR of 0.29 (95% CI, 0.21–0.41;  $P < 0.001$ ) and 0.44 (95% CI, 0.31–0.62;  $P < 0.001$ ), indicating that the risk to develop only circulatory symptoms in contrast to only respiratory symptoms is low if food and drugs are the elicitors of anaphylaxis.

When patients with atopic manifestations but without CVD were considered, they showed a decreased risk to develop only circulatory in comparison with respiratory symptoms (aOR = 0.54; 95% CI, 0.40–0.73;  $P < 0.001$ ). For patients with CVD without atopy, no effect was seen to develop preferably cardiovascular symptoms (aOR = 1.13; 95% CI, 0.59–0.73). Gender did not influence the reactivity pattern in this cohort (aOR = 1.27; 95% CI, 0.98–1.64).

Similar results were obtained if the risk factors were analysed in groups 'simultaneous respiratory and circulatory symptoms' in comparison with 'respiratory symptoms' (Fig. 2B) and 'respiratory and circulatory symptoms' versus 'circulatory symptoms' group (Fig. 2C).

### Discussion

In this study, we investigated the symptom profile and the impact of risk factors on the development of severe symptoms

**Table 4** Clinical profile of patients (*n* = 2012) subdivided according to the formation of respiratory and circulatory symptoms

| Symptoms                                             | <i>n</i> (%)<br>Only respiratory<br>( <i>n</i> = 570, 28.3%) | <i>n</i> (%)<br>Only cardiovascular<br>( <i>n</i> = 653, 32.5%) | <i>n</i> (%)<br>Respiratory and cardiovascular<br>( <i>n</i> = 789, 39.2%) |
|------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------|
| <b>Age (in years)</b>                                |                                                              |                                                                 |                                                                            |
| Mean ± SD                                            | 27.5 ± 22.5                                                  | 48.0 ± 18.3                                                     | 44.0 ± 20.2                                                                |
| Range                                                | <1–82                                                        | <1–87                                                           | <1–87                                                                      |
| <b>Age in years, age groups</b>                      |                                                              |                                                                 |                                                                            |
| 0–9, children ( <i>n</i> = 240)                      | 144 (25.3)                                                   | 28 (4.3)                                                        | 68 (8.6)                                                                   |
| 10–17, adolescents ( <i>n</i> = 187)                 | 88 (15.4)                                                    | 35 (5.4)                                                        | 64 (8.1)                                                                   |
| 18–30, young adults ( <i>n</i> = 247)                | 69 (12.1)                                                    | 69 (10.6)                                                       | 109 (13.8)                                                                 |
| 31–50, adults ( <i>n</i> = 631)                      | 138 (24.2)                                                   | 227 (34.8)                                                      | 266 (33.7)                                                                 |
| 51–65, young seniors ( <i>n</i> = 473)               | 88 (15.4)                                                    | 191 (29.2)                                                      | 194 (24.6)                                                                 |
| >65, seniors ( <i>n</i> = 234)                       | 43 (7.5)                                                     | 103 (15.8)                                                      | 88 (11.2)                                                                  |
| <b>Sex</b>                                           |                                                              |                                                                 |                                                                            |
| Male ( <i>n</i> = 950)                               | 266 (46.7)                                                   | 318 (48.7)                                                      | 366 (46.4)                                                                 |
| Female ( <i>n</i> = 1062)                            | 304 (53.3)                                                   | 335 (51.3)                                                      | 423 (53.6)                                                                 |
| <b>Elicitors</b>                                     |                                                              |                                                                 |                                                                            |
| Insects ( <i>n</i> = 1014)                           | 160 (28.1)                                                   | 421 (64.5)                                                      | 433 (54.9)                                                                 |
| Food ( <i>n</i> = 488)                               | 242 (42.5)                                                   | 83 (12.7)                                                       | 163 (20.7)                                                                 |
| Drugs ( <i>n</i> = 336)                              | 92 (16.1)                                                    | 105 (16.1)                                                      | 139 (17.6)                                                                 |
| Unknown ( <i>n</i> = 108)                            | 53 (9.3)                                                     | 30 (4.6)                                                        | 25 (3.2)                                                                   |
| Others ( <i>n</i> = 66)                              | 23 (4.0)                                                     | 14 (2.1)                                                        | 29 (3.7)                                                                   |
| <b>Pre-existent diseases</b>                         |                                                              |                                                                 |                                                                            |
| None ( <i>n</i> = 940)                               | 227 (49.8)                                                   | 344 (52.7)                                                      | 369 (46.8)                                                                 |
| Cardiovascular diseases (CVD) only ( <i>n</i> = 292) | 42 (7.4)                                                     | 125 (19.1)                                                      | 125 (15.8)                                                                 |
| Atopy only ( <i>n</i> = 568)                         | 254 (44.6)                                                   | 113 (17.3)                                                      | 201 (25.5)                                                                 |
| CVD and atopy ( <i>n</i> = 79)                       | 21 (3.7)                                                     | 21 (3.2)                                                        | 37 (4.7)                                                                   |
| Others ( <i>n</i> = 133)                             | 26 (4.6)                                                     | 50 (7.7)                                                        | 57 (7.2)                                                                   |

in anaphylactic patients. We observed high risks regarding the outcome of anaphylaxis in relation to age, the elicitors themselves and the presence of atopic diseases.

An advantage of our study is the large number of patients, whose anaphylactic events were recorded in a standardized manner after the diagnostic work-up by an allergist. Until now, most studies were designed to investigate the severity of anaphylaxis via a grading system (9, 13–16) rather than the symptom profile. A limitation of our study may be that most patients received medical treatment at the onset of the reaction, which may have influenced the outcome.

We identified insect venom as the most common trigger of anaphylaxis in our cohort. This result was also seen in a previous published study from Switzerland (3). The range of elicitors may depend on the geographical areas of data assessment as in the United States and Latin America, food and drugs are reported to occur more frequently (17–19). However, it has to be considered that in Germany, Austria and Switzerland, patients with insect venom-induced anaphylaxis are preferentially referred to specialized clinics for further diagnostics and treatment. As in the registry mainly allergy clinics are participating, a selection bias resulting in a high number of insect venom-induced anaphylaxis cannot be excluded. Furthermore, this inclusion of specialized centres ensures that the anaphylactic cases are evaluated carefully; however, patients who are not referred to the allergy centre are missed. Due to this fact and because other healthcare

givers (e.g. emergency doctors or private practices) did not participate in the registry, the data from the registry are not representative of anaphylaxis in the German-speaking area. The anaphylaxis registry serves as a clinical but not as an epidemiological registry.

The results of our regression model show an increasing risk to develop circulatory symptoms with increasing age. In younger age groups, the occurrence of respiratory symptoms dominates. This observation is inconsistent with a previous report where it was assumed that age has no impact on the symptom development (20). However, other reports described that infants and young children are more likely to experience respiratory compromise than hypotension or a cardiovascular shock (6, 8). Age as an important predictor of severe hypersensitivity reaction has been proposed previously (21). In that study, reactions graded as severe included cardiovascular and respiratory symptoms, with a dominance of patients having cardiovascular signs (65%) (21). In insect venom-dependent anaphylaxis, higher age was a risk factor (22), but not in food-induced anaphylaxis (21, 22). This indicates that both factors, age and the precise elicitor, have an impact on the clinical outcome of anaphylaxis.

Among the elicitor groups ‘food’, ‘drugs’, ‘other’ and ‘unknown’, the probability of developing respiratory symptoms in comparison with circulatory symptoms is very high. In particular, the comparison of single-organ manifestations – only respiratory versus only circulatory – hints in that

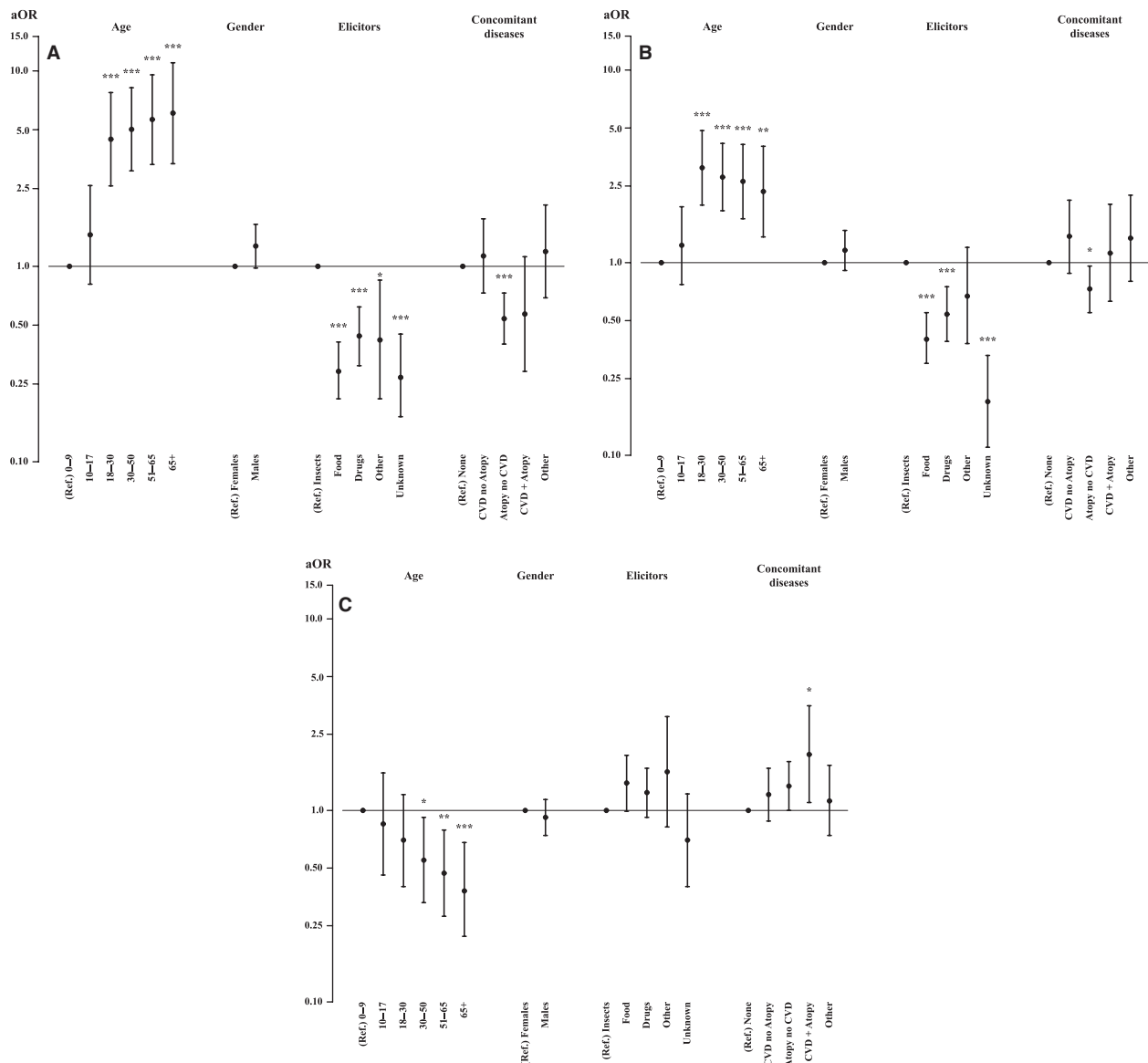


**Figure 2** (a) Risk factor profile of only respiratory symptoms vs only circulatory symptoms. Adjusted odds-ratios (aORs),  $\log_{10}$ -scale. aOR > 1: elevated risk of only circulatory symptoms, aOR < 1: elevated risk of only respiratory symptoms. \* $P$ -value < 0.05, \*\* $P$ -value < 0.01, \*\*\* $P$ -value < 0.001. (b) Risk factor profile of only respiratory symptoms vs combined respiratory and circulatory symptoms. Adjusted odds-ratios (aORs),  $\log_{10}$ -scale. aOR > 1: elevated risk of

combined respiratory and circulatory symptoms., aOR < 1: elevated risk of only respiratory symptoms. \* $P$ -value < 0.05, \*\* $P$ -value < 0.01, \*\*\* $P$ -value < 0.001. (c) Risk factor profile of only circulatory symptoms vs combined respiratory and circulatory symptoms. Adjusted odds-ratios (aORs),  $\log_{10}$ -scale. aOR > 1: elevated risk of combined respiratory and circulatory symptoms., aOR < 1: elevated risk of only circulatory symptoms. \* $P$ -value < 0.05, \*\* $P$ -value < 0.01, \*\*\* $P$ -value < 0.001.

direction. The analysis of the combined symptoms points into the same direction but with a weaker impact. By contrast, the elicitor insect venom tends to the opposite; here, the development of circulatory symptoms is statistically more likely. With regard to the elicitor food, our results confirm previous data, suggesting that food-induced anaphylactic reactions are dominated by respiratory compromise, although in this report fatal reactions were studied exclusively (20).

Likewise for insect venom, our results are comparable, indicating a predominance of cardiovascular symptoms for this type of elicitor. However, among drug-induced anaphylaxis, we observed a higher risk of respiratory symptoms.

The analysis of concomitant diseases in the regression model shows that patients with atopic diseases are at a significantly decreased risk of developing circulatory symptoms. This suggests that patients suffering from an atopic disease are more

likely to develop respiratory than circulatory compromise during an anaphylactic reaction. It is known that asthma is a risk factor for a severe allergic reaction with the preferential development of respiratory symptoms (20, 23). Recently, also allergic rhinoconjunctivitis and atopic dermatitis have been associated with an increased risk of anaphylaxis (23).

In our regression model, CVD had no impact of the development of anaphylactic symptoms. In contrast, in literature, it has been suggested that cardiomyopathies may increase the risk of cardiac impairment during an allergic reaction (24). On the other hand, Brown showed that cardiovascular comorbidities were not significantly associated with severe reaction features, supporting our findings (21). Nevertheless, to assess the impact of CVD on anaphylaxis, further investigations in more detail are necessary.

In conclusion, our results show that the occurrence of circulatory symptoms during an anaphylactic reaction is associated with age and insect venom-induced anaphylaxis. The development of respiratory symptoms is more likely if the reaction is caused by food and if the patients suffer from another IgE-dependent allergy. Taken together, the onset of life-threatening respiratory and circulatory symptoms is determined by specific risk factors. Our data system has been shown to be suitable to obtain data from allergy centres in central Europe and can therefore be used throughout Europe in the future. A pan-European pilot phase has been recently started and will provide more data about anaphylaxis in Europe.

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### Authors' contributions

M. Worm designed the study. S. Hompes monitored data collection. G. Edenharter and S. Hompes analysed the data, and G. Edenharter created the figures. Data evaluation was made by F. Rueff. S. Hompes did the literature search and wrote the first draft of the article. S. Hompes and M. Worm interpreted the data and drafted the article. The majority of the data were provided by F. Rueff, K. Scherer, C. Pföhler, V. Mahler, R. Treudler, R. Lang, K. Nemat, A. Köhli and S. Hompes. The manuscript was revised by F. Rueff, K. Scherer, C. Pföhler, V. Mahler, R. Treudler, R. Lang, K. Nemat, A. Köhli and B. Niggemann. All authors approved the final report.

### Conflict of interest

F. Rueff has received lecture fees from ALK-Abelló and Phadia. R. Treudler has received consultancy fee from

ALK-Abello, lecture fees from ALK-Abello, Allergopharma, MSD, Pfizer, Merckle-Ricordatl, Novartis and travel expenses from ALK-Abello, Shire, Stallergens, Pfizer and MSD. M. Worm has received consultancy fees from Allergopharma and ALK-Abello. The rest of authors declare that they have no competing interests.

### Appendix

The following centres are member of the anaphylaxis registry (ANAPHYLAXIE.net) and have contributed cases to this publication: U. Rabe, Clinic of Pneumology, Johanniter-Hospital Treuenbrietzen, Germany; M. Henzgen, Pneumology/Allergology of the Department of Internal Medicine I, Friedrich-Schiller-University Jena, Germany; E. Coors, Department of Dermatology and Venerology, University Medical Center Hamburg-Eppendorf, Germany; W. Aberer, Department of Dermatology, Medical University of Graz, Austria; L. Lange, Children's Hospital, St. Marien-Hospital Bonn, Germany; B. Wedi, Department of Dermatology, Hannover Medical School, Germany; H. Dickel, Department of Dermatology and Allergology, Ruhr-University Bochum, Germany; P. Schmid-Grendelmeier, Department of Dermatology, University Hospital of Zurich, Switzerland; T. Reese, Children's Hospital, Mathias-Spital Rheine, Germany; G. Hansen, Department of Paediatric Pneumology and Neonatology, Hannover Medical School, Germany; T. Kinaciyan, Department of Dermatology and Centre of Physiology and Pathophysiology, Medical University of Vienna, Austria; P. Eng, Paediatric Pulmonology and Allergy/Immunology, Children's Hospital Lucerne, Switzerland; T. Bieber and J. Hanf-land, Department of Dermatology, University Hospital Bonn, Germany; K. Beyer, Department of Paediatric Pneumology and Immunology, University Hospital Charité Berlin, Germany; P. Eng, Paediatric Pulmonology and Allergy/Immunology, Children's hospital Aarau, Switzerland; M. Rett, Children's Hospital, Clinic Itzehoe, Germany; N. Hunzelmann, Department of Dermatology and Venerology, University Hospital of Cologne, Germany; J. Fischer, Department of Dermatology, University of Tuebingen, Germany; M. Kopp, Department of Dermatology and Allergy, University of Luebeck; H. Merk, Department of Dermatology, University Hospital Aachen, Germany; T. Fuchs, Department of Dermatology, Venerology and Allergy, Georg-August-University Goettingen, Germany; E. Varga, Department of Paediatrics, Medical University of Graz, Austria; F. Riffelmann, Allergology Unit, Hospital Kloster Grafschaft/Schmallenberg, Germany; A. Nordwig, Children's Hospital Dresden-Neustadt, Dresden, Germany; Z. Szeplasi, Department of Paediatrics, Medical University of Vienna, Austria; R. Bruns, Department of Paediatrics, Ernst-Moritz-Arndt-University of Greifswald, Germany; R. Guggenheim, Department of Paediatrics, Triemli City Hospital Zurich, Switzerland; I. Yildiz, Children's Hospital, Friedrich-Ebert-Hospital Neumuenster, Germany; S. Thies, Department of Dermatology and Allergy, Asklepios Hospital Uckermark Schwedt, Germany; T. Spindler, Waldburg-Zeil Hospitals, Department of Paediatrics, Clinics Wangen im

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