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Factors increasing the risk for a severe reaction in anaphylaxis: An analysis of Data from The European Anaphylaxis Registry

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Abstract

Background: Preventive measures to decrease the frequency and intensity of anaphylactic events are essential to provide optimal care for allergic patients. Aggravating factors may trigger or increase the severity of anaphylaxis and therefore need to be recognized and avoided.

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Objective: To identify and prioritize factors associated with an increased risk of developing severe anaphylaxis.

Methods: Data from the Anaphylaxis Registry (122 centers in 11 European countries) was used in logistic regression models considering existing severity grading systems, elicitors, and symptoms to identify the relative risk of factors on the severity of anaphylaxis.

Results: We identified higher age and concomitant mastocytosis (OR: 3.1, CI: 2.6 - 3.7) as the most important predictors for an increased risk of severe anaphylaxis. Vigorous physical exercise (OR: 1.5, CI: 1.3 - 1.7), male sex (OR: 1.2, CI: 1.1 - 1.3), and psychological burden (OR: 1.4, CI: 1.2 - 1.6) were more often associated with severe reactions. Additionally, intake of beta-blockers (OR: 1.9, CI: 1.5 - 2.2) and ACE-I (OR: 1.28, CI: 1.05, 1.51) in temporal proximity to allergen exposition were identified as important factors in logistic regression analysis.

Conclusion: Our data suggest it may be possible to identify patients who require intensified preventive measures due to their relatively higher risk for severe anaphylaxis by considering endogenous and exogenous factors.

Key words Age, anaphylaxis, logistic regression, mastocytosis, risk factors,

Introduction

Anaphylaxis is a potentially life-threatening condition with an increasing incidence [1]. Therefore, preventative measures and mitigating enhancing factors may decrease the frequency and intensity of anaphylaxis to improve patient care. More knowledge about elicitation and augmentation factors may allow physicians to better advise patients how to avoid serious anaphylactic episodes either by prophylactic measures or by immediate access to medication (given by others or self-administered by educated patients). Aggravating factors, also called augmentation factors or cofactors, may increase the severity of a reaction or even may elicit a reaction to an allergen that would normally not appear in the absence of a given cofactor (i.e. physical exercise [2], or drug-intake [3]). Moreover, certain concomitant diseases e.g. mastocytosis may affect the initiation, and also severity of anaphylaxis. Prospective studies about such co- and risk factors which may increase the severity of anaphylaxis are limited due to the acute and dangerous nature of this condition.

The severity of anaphylaxis remains difficult to quantify, as physicians evaluate primarily the presence of qualitative symptoms. Objective quantitative laboratory tests are currently not established and therefore multiple grading systems for assessing the severity of anaphylactic events have been developed (e.g. by Brown [4], Muraro [5], Mehl [6], Müller [7]). We focused our exploratory analysis on the grading system of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis

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Network (NIAID/FAAN) [8] and the Ring and Messmer grading system [9]. The first one divides anaphylactic events into "severe", and "non-severe" cases and the latter one provides four levels of severity (grades I - IV). Although these systems lack specificity, and have not been validated their accessibility makes them widely used in clinical practice in northern America and central Europe.

Within the present data analysis we sought to describe and prioritize factors associated with an increased risk of severe anaphylactic reactions to provide a basis for better identification and avoidance of the most important ones in clinical practice.

Methods

Database and cohort

In this study, the data from the European Anaphylaxis Registry [10] (status for May 2017) was analyzed. Briefly, the registry gathers cases of immediate hypersensitivity reactions reported by trained professionals from 122 centers (of which 47 were pediatric centers) in 11 European countries (Austria, Bulgaria, France, Germany, Greece, Ireland, Italy, Poland, Spain, Slovenia and Switzerland). The online data entry system uses a questionnaire developed by an expert panel [11] and gathers clinical data from medical reports supplemented by patient's history. It covers pseudonymized patients medical data on the symptoms of anaphylaxis, along with the course of treatment and future episodes prophylaxis. The study was approved by the Ethics Committee at Charité - Universitätsmedizin Berlin (the coordinating center) and by the local Ethics Committees in all participating countries.

For this analysis, data about factors which can influence the severity of anaphylaxis (i.e. eliciting factors, concomitant diseases, medications, and lifestyle) were used for logistic regression modelling. We limited the cohort to cases meeting the definition of anaphylaxis by NIAID/FAAN [8]. We excluded repeated reactions of patients who had more than one reported reaction to avoid violation of the logistic regression assumptions. Therefore, only the first reported event of anaphylaxis was included in the final database from patients who had multiple reactions.

We included eliciting factors in the models and grouped elicitors of anaphylaxis into four categories: food, drug, insect venom, and other elicitors (which consisted of known elicitors not belonging to previous groups and idiopathic elicitors).

Statistical analysis

Logistic regression was performed to identify factors increasing the risk of developing severe anaphylaxis. Incomplete case entries in the database were excluded. To achieve the best modelling of logistic regression we used the following procedure:

1. We defined outcome variables as severity grades: a) according to NIAID/FAAN, anaphylaxis was classified as “severe” if hypoxemia, hypotension, collapse, altered consciousness, or incontinence was present; b) Ring and Messmer grading system

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restricted to only two levels of mild to moderate anaphylaxis (grades II, and III) and severe reactions (grade IV).

2. We included the following predictor variables in the initial models: age, sex, concomitant diseases (rhinitis, asthma, atopic dermatitis, cardiac disorders, mastocytosis, thyroid disorders, infection), concomitant medication (ACE-I, ASA, AT2, beta-blocker), reaction elicitor (restricted to food, insect venom, drugs, and "other"), lifestyle (physical exercise intensity and psychological stress level), and whether it was a first or subsequent anaphylaxis episode in a given patient.
3. We verified that selected predictors were not violating the assumptions of logistic regression i.e. (1) we checked for similar variables closely correlated variables (Cramer's V > 0.25) and included only one of them; (2) excluded variables that may not have the mechanistic role in the severity of anaphylaxis.
4. Generalized linear models of binomial dependent variable were created for NIAID/FAAM and Ring and Messmer (restricted to two levels) severity gradings using the "glm" function from the "stats" package [12].
5. Models underwent a predictor selection process using step-wise elimination of the non-significant predictors by comparison of the model's calculated Akaike Information Criterion (AIC).
6. We removed the predictors which had a negligible impact to obtain models with minimal sets of predictors, as advised in the SAMPL guidelines [13].
7. The resulting final models were reported in figures and tables and used for subsequent analyses.

The reporting of regression results conforms with the EQUATOR Network's SAMPL Guidelines [13] and includes the recommendations from Peng et al. [14]. We used The R software package for statistical analysis [12]. Variable importance was determined using mean z-values of multiple regression models. We defined statistical significance as $\alpha = 0.05$.

Results

Out of 10212 total cases registered in the European Anaphylaxis Registry (status from March 2017) 8055 met the definition of anaphylaxis according to the NIAID/FAAN Criteria [8]. 201 (2.5%) cases were reported as a second reaction from the same patient, and were analysed separately. Three elicitors of anaphylaxis (food, drugs and insect venom) were the main causes for these hypersensitivity reactions. Insect venom was the most frequently reported cause of the reactions. Cases with unknown values among other predictors (538; 6.85%) were not included to ensure highest quality of statistical models. After selecting the cases as described above (Fig. 1), a database with 7316 patients aged 0 - 93 years was identified (48.4% males and 51.6% females; 28.9% children and 71.1% adults). Large number of missing values (854, 11.67%) regarding the "alcohol intake" variable prevented us from incorporating in into further analysis. Concomitant cardiologic conditions correlated with the concomitant use of beta blockers (Cramer's V = 0.55), ASA (Cramer's V = 0.3) and ACE-I (Cramer's V = 0.49) drugs. Therefore we discarded this variable and decided to include concomitant medications into the analysis.

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Age is the dominant risk factor for severe anaphylaxis

Age was the most important predictor when performing the multivariable analysis (Fig. 2 and 3). Each year was associated with 1.6% (CI: 1.4% - 1.9%) increase in the odds of experiencing a severe anaphylactic event, given that all other variables were held equal (Table 1, S1 and S2). The relation of increasing odds of severe anaphylaxis to age was most evident in the NIAID/FAAN severity grading in patients aged 13-56 years (Fig. 2) and did not follow the linear relationship at age extremes. In the Ring and Messmer grading system patients over 70 years old had significantly more severe reactions (Fig. 2).

The age of patients who experienced serious anaphylaxis varied significantly between these models (Ring and Messmer mean age in grade IV cases: 49.96; NIAID/FAAN mean age in severe cases: 42, p-value < 0.0001).

Male sex

Male sex was associated with a higher risk of severe anaphylaxis (OR: 1.16 and 1.92 in NIAID/FAAN and Ring and Messmer grading based models respectively). This represents a consistent finding between both anaphylaxis models (Table 1), although this relationship was not illustrated by a simple Chi^2 test (p-value = 0.1187; Table S1).

Mastocytosis

Mastocytosis was a concomitant disease in 120 patients, (1.64% of all cases in our database, tables S1 and S2). Patients with mastocytosis had 1.59 times higher crude (other factors not accounted for) relative risk of developing a more serious anaphylaxis response than non-mastocytosis patients.

Regression models for both severity grading systems revealed that mastocytosis increased the odds of developing severe anaphylaxis. Patients who were diagnosed with mastocytosis had a 3.19, (CI: 2.66 - 3.73) and 5.46, (CI: 4.89 - 6.06) times higher odds for developing more severe anaphylaxis than subjects without indication of mastocytosis (according to the NIAID/FAAN and Ring and Messmer severity grading based regression models). Mastocytosis increased the risk (p < 0.0001) of severe anaphylaxis in the venom-elicited cases.

Concomitant medication

Independent from the elicitor, the concomitant intake of drugs like beta blocker 1.857, (CI: 1.47 - 2.25) or ACE-inhibitors 1.28, (CI: 1.05 - 1.51) increased the risk to develop severe anaphylaxis. ASA or AT-2 intake did not increase the risk in both regression models.

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Vigorous exercise

The NIAID/FAAN grading system based model included exercise level as an important variable in the selection process. Patients who reported vigorous exercise during (or prior to) a given reaction had a higher risk to develop severe anaphylaxis 1.48, (CI: n1.28 - 1.67) in comparison to non-physically-active patients (reference level). Dissecting this cofactor to the main elicitor groups (food, insects and drugs) the models restricted to drugs and food indicated vigorous exercise to be associated with a higher risk to develop more severe anaphylaxis (OR = 3.5, p value = 0.03 and OR = 2.06, p value = <0.0001 respectively). When the model was restricted to food this risk was corresponding to the level of exercise (higher reported exercise level - higher risk of developing a severe reaction.

Psychological burden

Patients, who in the physician's opinion, had a clinically relevant psychological burden preceding the reaction had a 1.40, (CI: 1.19 - 1.61) times greater odds of developing more severe anaphylaxis than their counterparts (Table 1 and S1).

Concomitant infection

In 257 cases physicians reported an active infection concomitant to anaphylaxis (e.g. upper respiratory tract infection or common cold). 52.14% of these patients had a severe anaphylaxis. Infection failed to be considered significant in any of our models.

Concomitant asthma

The model based on NIAID/FAAN grading indicated that asthmatic patients had a rather lower risk of developing serious anaphylaxis (OR: OR: 0.75, CI: 0.61 - 0.88; table S1). However, this predictor was insignificantly increasing the risk in the Ring and Messmer grading based model (OR = 1.43, (CI: 1.01 - 1.84); p = 0.09).

Elicitors of anaphylaxis

When the model was based on the NIAID/FAAN grading system, insect stings were identified as a factor aggravating the severity of anaphylaxis when compared to a non-homogeneous group of various (non-food-induced and non-drug-induced) elicitors (OR = 2.43, p-value = <0.0001). However, these findings were not confirmed in the Ring and Messmer model (OR = 0.88, p-value = 0.67) since insect venom did not prove significance in this model. Insect venom (which in our database was mostly due to yellow-jackets 67.95% and bees 21.11% of all insect induced events) was recognized as an elicitor in 2743 cases. Yellow-jacket-sting-elicited anaphylaxis cases were more often severe than bee-sting-elicited cases (66.49% vs. 73.07%; p = 0.0026).

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Drugs as elicitors of anaphylaxis were included in both regression models and indicated that, if a reaction was elicited by drugs, the reaction was more likely to be severe (OR: 1.43, CI: 1.23 - 1.62). The values were consistent with these in the Ring and Messmer model. OR: 2.29, (CI: 1.73 - 2.86). These findings suggest that drugs as elicitors of anaphylaxis, though being a non-homogeneous group of elicitors increase the on the severity of a reaction.

Discussion

The present data, based on a large scale data set from the European Anaphylaxis Registry, enable weighting of intrinsic and extrinsic factors which may facilitate or aggravate anaphylaxis. These can be differentiated into [11], of the intrinsic factors higher age, male sex, and concomitant mastocytosis were dominant predictors for severe anaphylaxis. Vigorous exercise, vulnerability to psychological burden and drugs (i.e. beta-blockers and ACE-I [15]) made for the significant extrinsic ones. Although these factors have been previously reported to play a role in aggravating anaphylaxis (based on single cases or case series) their frequency and relative risk have never been proven in a logistic regression model using data from a large cohort of anaphylaxis patients before. Elicitors of anaphylaxis have an essential impact on the reaction's severity [16] and were therefore significant extrinsic predictors.

Van der Linden et al. have previously shown that older age correlated with severe anaphylaxis (grade IV of the Ring and Messmer scale) [17] in patients stung by insects. Similar to these findings, a study by the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity suggested older age as a factor associated with more severe reactions [18]. This is in line with the present analysis, and previous findings from the Anaphylaxis Registry on a smaller sample size [16]. Although in higher age groups cardiovascular and other diseases were present more frequently, the age related increase in severity might be related to mast cell specific factors. Nguyen et al. suggested that mast cell degranulation pathways change with age [19] what could explain the observations in our study. Note that the effect of age is calculated for each year of life, meaning that the OR value (1.6%) has to be multiplied by patient's age to illustrate the factual odds of a severe anaphylaxis compared to baseline.

A previous study from Ruëff et al. [18], investigated insect venom allergic patients and indicated male sex as a risk factor for severe anaphylaxis. The authors explain this by different exposure pattern to insects in men and women, but our analysis suggests that male sex is a risk factor for severe anaphylaxis independent from the elicitor as it is also observed in anaphylactic reactions caused by drugs or food. Although there are publications suggesting that female sex hormones are connected to more severe reactions in mice [20] and humans [21], the above evidence of large-cohort-studies put these findings in question [22].

Concomitant cardiac conditions were an important predictor of severe anaphylaxis in the analysis restricted to food-elicited reactions. Although this group of diseases is not homogeneous, previous data on cardiac mast cells suggest that mast cell degranulation in the heart can induce life threatening symptoms [23]. Cardiomyopathy has been reported to be associated with increased mast cell numbers [24], as well as with an

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increased local release of fibrogenic factors (e.g. histamine, tryptase, and leukotriene C4) may contribute to collagen accumulation in the submucosal tissue of the heart in patients with cardiomyopathy [23].

The majority of patients with increased mast cell numbers due to mastocytosis have an increased tryptase concentration in their serum, which is a risk factor for severe anaphylaxis [25, 26]. Previous reports suggested that mastocytosis is a potential factor increasing the risk of severe immunoglobulin (Ig)E dependent anaphylaxis [27] as it had been linked to fatal reactions in patients stung by Hymenoptera. Our data support these findings indicating that mastocytosis is one of the most potent cofactors for severe anaphylaxis. The European Anaphylaxis Guidelines recommend the prescription of an adrenaline auto-injector for self-treatment of anaphylaxis in mastocytosis patients [28]. Moreover, life-long systemic immune therapy should be considered in venom allergic patients with mastocytosis to prevent life-threatening anaphylactic episodes [29].

Surprisingly, our analysis suggested opposing direction of association between asthma and severity of anaphylaxis in two regression models. This observation might be explained by the possibility that such patients might already receive anti-allergic medications or had a better access to anti-allergic drugs. Also, their ability to better self-diagnose and self-medicate episodes of hypersensitivity reactions (which therefore do not develop into a full-blown anaphylactic response) can be discussed and requires further clinical studies. However, the level of asthma management was not included into the Registry's questionnaire.

We have shown that vigorous exercise reported by the patient seems to be linked to a higher risk of developing severe anaphylaxis, again most importantly, independent from the trigger factor. Exercise was previously indicated as a factor which can trigger reactions that would otherwise not progress to anaphylaxis. [30]. Food dependent, exercise induced anaphylaxis (FDEIA) was earlier recognized as a disease entity [31] but the role of exercise in reactions induced by drugs and insects is not well understood. Thus, we identified exercise as a significant factor increasing the risk for severe drug-induced anaphylaxis. This might be based on a similar mechanism as in FDEIA, with lowering the degranulation threshold of mast cells and resulting in severe reactions due to a higher abundance of anaphylactic mediators.

Emotional burden contributed to the severity of anaphylaxis as well. Due to the inability to objectively quantify emotional burden, we left it to the opinion of the physician to indicate whether emotional burden was clinically relevant in a given case. This evaluation was questionable in young children (< 3 year-olds). However, it was unlikely to influence the study results as we only had 7 (1.4%) such responses. There is evidence that the central nervous system can regulate the secretion of mast cell mediators in rats [32]. A study performed in mice has shown an increase of severity in passive systemic anaphylaxis when the animals were exposed to electrical shocks. Following these finding Yang et al. [33] suggested that chronic psychological stress in rats promotes intestinal sensitization to gut pathogens but no comparable human studies are available.

Drug-elicited anaphylaxis posed a higher risk to develop severe anaphylaxis when compared to the other elicitors like food and insect venom. It is important to distinguish the cases of anaphylaxis induced by drugs from those that are exacerbated by drugs. Our analysis indicated that the concomitant use of beta blockers and ACE-I may

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contribute to the risk of developing a severe anaphylactic response independently from the elicitor. Concomitant drug intake influence is however not consistent in all the regression models. These factors may play a role in different sub-populations of patients, and additionally, are most likely influenced by the non-heterogeneous group of concomitant diseases (e.g. hypertension, congestive heart failure but also arrhythmia or diabetes) for which these medications are used. On the other hand, it was recently shown that beta-blockers and the ACE-inhibitor ramipril can directly promote mast cell activation [15] and are associated with increased odds for severe anaphylaxis.

A limitation of the European Anaphylaxis Registry is the lack of a corresponding control group. Therefore, we cannot draw inferences which factors are increasing the risk of developing anaphylactic responses in general. A potential confounder of the severity of anaphylaxis is the treatment itself, which decreases the severity of the symptoms if administered quickly. This way, an immediately treated patient with a potentially lethal response might be classified as only having milder symptoms due to the prompt administration of epinephrine. Moreover, low number of fatal cases of anaphylaxis in our registry (due to lack of referencing from the emergency departments) may skew the analysis results. The results in NIAID/FAAM and Ring and Messmer based models were similar and slight differences were expected due to non-uniform division of severity grades in these models.

Taken together, our data enabled us for the first time to calculate the relative risk of endogenous and exogenous factors influencing the severity of anaphylaxis based on a large dataset.

Author contributions

Margitta Worm and Sabine Dölle performed conceptualization and design of the study, managed data acquisition, wrote the original manuscript and revised it critically.

Jean-Marie Renaudin, Maria Beatrice Bilo, Victòria Cardona, Kathrin Scherer Hofmeier, Alice Köhli, Andrea Bauer, George Christoff, Ewa Cichocka-Jarosz, Thomas Hawranek, Jonathan O'B Hourihane, Lars Lange, Vera Mahler, Antonella Muraro, Nikolaos G Papadopoulos, Claudia Pföhler, Iwona Poziomkowska-Gęsicka, Franziska Ruëff, Thomas Spindler, Regina Treudler, Montserrat Fernandez-Rivas acquired the data and revised the manuscript critically for important intellectual content.

Wojciech Francuzik wrote the original manuscript and revised it critically as well as performed the data analysis.

All authors approved the final version of the manuscript for publication.

Conflict of interest

Sabine Dölle declares Support for travel to meetings for the study from NORA e.V. Montserrat Fernandez-Rivaz recieved Support for travel to meetings for the study from NORA e.V. Ouside the submitted work she declared Consultancy for the AImunne, Reacta Biotech, Employment at the Hospital Clinico San Carlos, Grants to her institution from the Eropean Commission and the Spanish Government: European Grants: FAST

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Figures

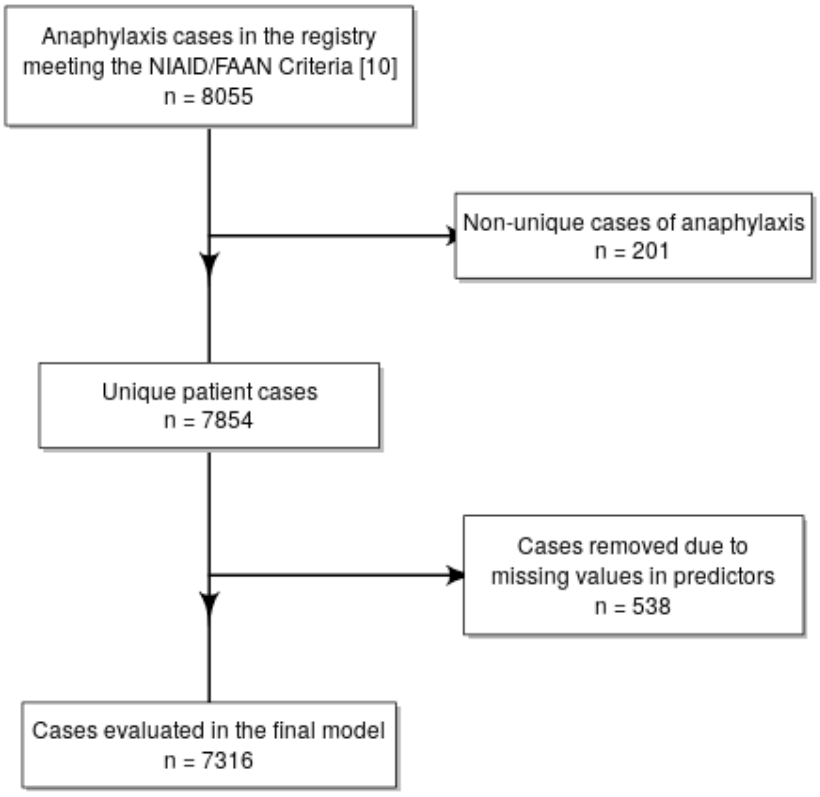


Figure 1: Flow diagram of final database creation process. Study algorithm illustrating the selection logic of cases used for further analysis.

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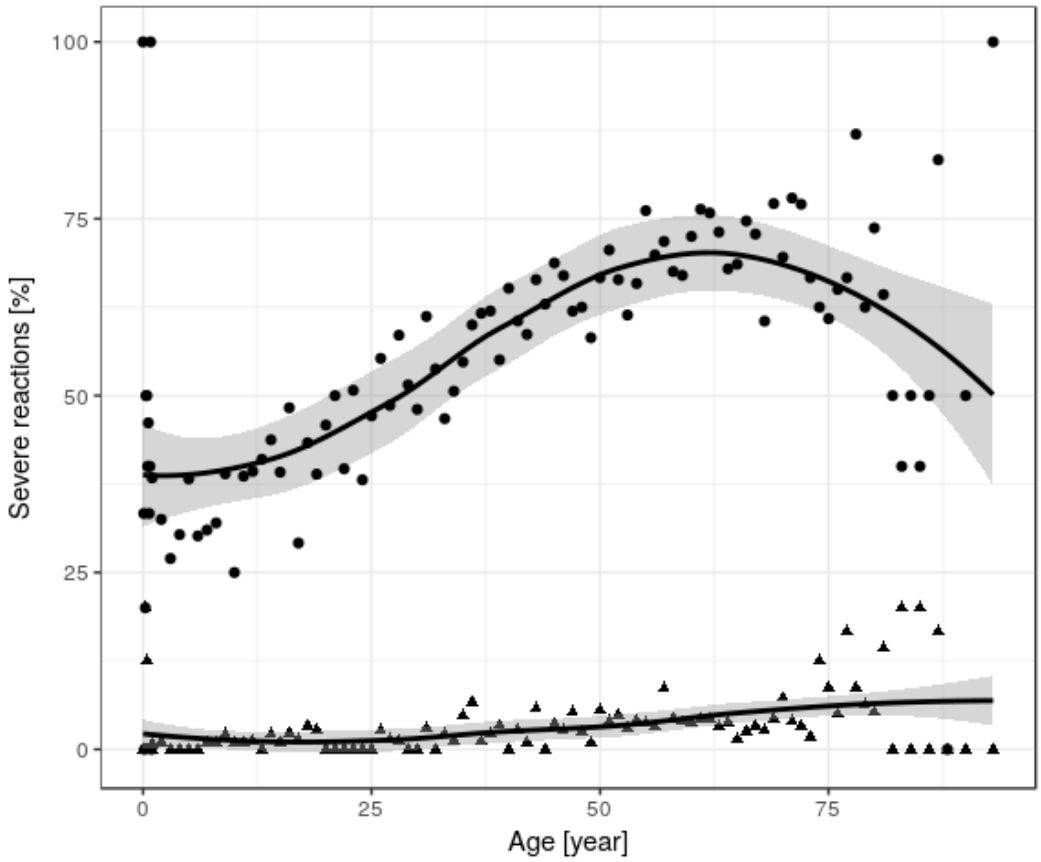


Figure 2. Age as a predictor of the severity of anaphylaxis. Data points represent the fraction of severe reactions in a given year of life. Dots: NIAID/FAAM definition of anaphylaxis. Triangles: Ring and Messmer's anaphylaxis severity scale. Solid curves: fitted Loess curves with 95% confidence intervals in grey.

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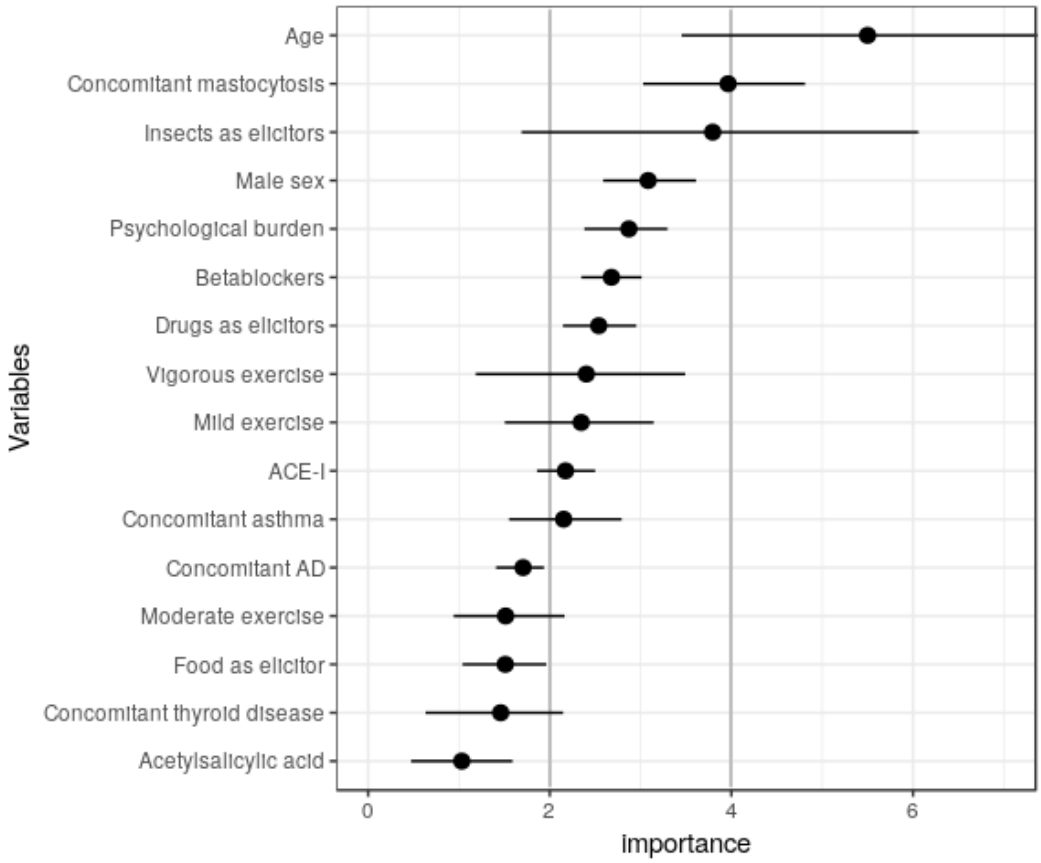


Figure 3: Variable importance plot integrating the anaphylaxis severity models. The importance value represents mean z-values across all designed models and is considering the relative influence of a given predictor on the outcome variable for each model. Whiskers represent 95% CI.

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Tables

	NIAID/FAAM		R&M II+III vs. IV	
	Coefficients	Odds Ratios	Coefficients	Odds Ratios
Age	0.017***	1.017***	0.019***	1.019***
	(0.014, 0.020)	(1.015, 1.020)	(0.010, 0.027)	(1.010, 1.028)
Male sex	0.147***	1.158***	0.652***	1.920***
	(0.044, 0.249)	(1.056, 1.260)	(0.346, 0.958)	(1.614, 2.226)
Concomitant asthma	-0.290***	0.748***	0.355*	1.425***
	(-0.429, -0.152)	(0.610, 0.887)	(-0.058, 0.767)	(1.013, 1.838)
Concomitant mastocytosis	1.161***	3.192***	1.700***	5.475***
	(0.628, 1.693)	(2.660, 3.725)	(1.113, 2.288)	(4.888, 6.063)
Concomitant thyroid disease	-0.233**	0.792***	Not used	Not used
	(-0.432, -0.034)	(0.593, 0.991)		
Mild exercise	-0.278***	0.757***	Not used	Not used
	(-0.454, -0.103)	(0.582, 0.932)		
Moderate exercise	0.088	1.092***	Not used	Not used
	(-0.108, 0.284)	(0.896, 1.288)		
Vigorous exercise	0.389***	1.475***	Not used	Not used
	(0.195, 0.583)	(1.281, 1.669)		
Psychological burden	0.336***	1.399***	0.839***	2.314***
	(0.124, 0.547)	(1.187, 1.611)	(0.413, 1.265)	(1.888, 2.740)
ACE-I	0.248**	1.282***		
	(0.015, 0.481)	(1.049, 1.514)		
Betablockers	Not used§	Not used	0.619***	1.857***
			(0.227, 1.011)	(1.465, 2.249)
Food as elicitor	-0.149*	0.861***	-0.649*	0.522
	(-0.327, 0.028)	(0.684, 1.039)	(-1.310, 0.011)	(-0.138, 1.183)
Drugs as elicitors	0.357***	1.428***	0.830***	2.294***
	(0.162, 0.551)	(1.234, 1.623)	(0.267, 1.394)	(1.731, 2.857)
Insects as elicitors	0.889***	2.432***	-0.123	0.884***
	(0.710, 1.068)	(2.253, 2.612)	(-0.690, 0.444)	(0.317, 1.451)
Constant	-0.815***	0.443***	-5.135***	0.006
	(-1.006, -0.624)	(0.252, 0.634)	(-5.796, -4.475)	(-0.655, 0.667)
Observations	7,316		7,316	
Log Likelihood	-4,537.394		-779.569	
Akaike Inf. Crit.	9,102.788		1,579.137	
Note:	*p<0.1; **p<0.05; ***p<0.01			

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Table 1: Regression coefficients of the models explaining the severity of anaphylaxis in two severity scales with predictors listed in the columns. The logistic regression coefficients represent the change in logit for each (unit) change in the predictor. Given that the logit is not intuitive we focused on odds ratios (OR) to evaluate the contribution of individual predictors. OR in two different regression models illustrate the association between co-factors of anaphylaxis and: A) NIAID/FAAN definition of anaphylaxis, and B) Ring and Messmer's Anaphylaxis severity scale (logistic regression models). § The predictor was proven insignificant in this model and was therefore excluded by the stepwise predictor selection algorithm.

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