Phenotype and risk assessment of insect venom anaphylaxis: a case - control study of the European Anaphylaxis Registry

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# Abstract

**Introduction:** Insect-venom elicited anaphylaxis is a common, life-threatening, hypersensitivity reaction. It is bound with specific: 1) symptom profile, 2) cofactors and 3) management. Identifying the diffeneces in subtypes of anaphylaxis is crucial for future management guidelines and personalized medicine approach.

**Methods:** Using data from the European Anaphylaxis Registry (12874 cases) we identified 3612 with insect-venom elicited anaphylaxis and analyzed these in comparison to sex-and-age-matched anaphylaxis cases triggered by other elicitors (n = 3613).

**Results:** Venom induced anaphylaxis (VIA) more frequently involed over 3 organ systems and was associated with cardiovascular symptoms what was most prominently visible in patients under 22 years of age. Absence of skin symptoms during anaphylaxis correlated with baseline serum tryptase and was associated with an increased risk of severe reaction specificaly in VIA. Intramuscular or intravenous adrenaline was administered significantly less often in IVA especially without prior history of anaphylaxis. Subelevated baseline serum tryptase (8-11.5 ng-ml) was more frequently associated with severe anaphylaxis and this effect was most prominantly visible for IVA.

**Conclusions:** Due to the specific symptom profile, frequently affecting cardiovascular system, patients undergoing IVA are undertreated with adrenaline. Lack of urticaria or flushing during previous anaphylaxis (especialy in combination with subelevated baseline serum tryptase levels) is associated with severe reactions.

# Introduction

Hypersensitivity to insect venom is a systemic reaction (anaphylaxis) in up to 0.3–7.5% of the adult population [1]. Venom induced anaphylaxis (VIA) can be fatal, and patients sometimes require lifelong systemic immunotherapy [2]. The need for a more precise description of the diagnosis, identification of biomarkers, and phenotypes of anaphylaxis is discussed [3]. Nevertheless, in order to facilitate a precision-medicine approach [4] for the diagnosis of anaphylaxis — a better understanding of its clinical subtypes is required.

Controlled clinical trials in anaphylaxis are hardly possible due to the acuteness of this life-threatening condition and their infrequent and random occurence. Therefore registries, gathering clinical data from patients with a well documented (recent) history of anaphylaxis are crucial in investigating this entity.

This study aimed to identify clinical patterns of venom induced anaphylaxis (VIA) regarding symptoms, cofactors, and management by a case-control comparison with other types of anaphylaxis (non-VIA).

# Methods

We searched the European Anaphylaxis Registry [5] (status from March 2019) for anaphylaxis cases elicited by insect’s venom. The flowchart in Fig. 1A represents the detailed case-selection process.

The diagnosis of anaphylaxis was based on the definition by NIAID/FAAN [6] and the severity according to Ring and Messmer Scale [7]. Grades III and IV (presenting with significant hypoxia, hypotension, confusion and loss of consciousness, or incontinence or cardiac arrest) were considered severe.

Due to a large number of documented reactions in the European Anaphylaxis Registry - we were able to match the VIA with non-VIA cases according to sex and age to reduce the comparison bias. When we analyzed a density plot of VIA cases according to age - we determined a bimodal distribution forming two subsets of patients with a cutoff age of 22 (Fig 1B). Subsequently, we compared the management in both groups and matched the control group according to the severity of a reaction. Propensity score matching has been performed using the “MatchIt” package for R [8]. The results of the propensity score matching are in Fig. 1B-D and supplementary Fig 7.

The final database consisted of 3612 cases of venom induced anaphylaxis reported from allergy centers in 11 countries and sex-and-age matched control group. We compared the frequency of various symptoms, cofactors — known to increase the risk of severe anaphylaxis, [9] and management in both groups.

Based on the severity and symptom profile, we defined a sub-elevated baseline serum tryptase (BST) cut-off value of 8 - 11.5 ng/ml (Fig. 4B).

We used the R Statistical Package [10] for statistical analysis. A simple comparison of categorical variables was performed using either Chi2 test or Fisher’s exact test (where the number of observation in a bin was less than 10). Continuous variables were analyzed using Mann-Whitney U test. In case of comparisons with two or more independent variables, we used Factorial ANOVA or Generalized Linear Models. We defined statistical significance as α = 0.05. Data, along with the analysis script, can be accessed online at <https://github.com/wolass/venomanaphylaxiscompendium>.

We trained a random forest classifier (using the “randomForest” package for R [11]) in order to find therapeutic approaches that varied the most between VIA / non-VIA group and presented the results Gini importance [12]. We also performed an association study of therapeutic interventions and symptoms. The resulting phi values are presented in a heatmap with automatic clustering using Ward’s Agglomerative Hierarchical Clustering with Euclidean distances [13].

# Results

## VIA is associated with cardiovascular symptoms

VIA displayed a specific symptom pattern. Patients, who underwent VIA, more often experienced cardiovascular symptoms (dizziness, hypotension, unconsciousness, reduced alertness) than patients with anaphylaxis due to other elicitors and less often presented with expiratory distress, rhinitis or diarrhoea (Fig. 2A).

Although the pattern of organ involvement during anaphylaxis in both groups showed similarities in gastrologic, skin, and respiratory systems, VIA more frequently involved over three organ systems (65.4% vs. 55.3%, Fig. 2B).

Younger patients (under 22) presented even more prominent differences in hypotension symptoms and significantly less frequently reported gastrointestinal symptoms (e.g. vomiting) when the reaction was triggered by insect venom.(Fig. 2C-E)

## Absence of skin symptoms during anaphylaxis is associated with more severe episodes of VIA

We found that 54.3% of patients with concomitant mastocytosis had anaphylaxis without skin symptoms (i.e. urticaria and flushing) which was significantly more compared to patients without diagnosed mastocytosis (30.9%, p < 0.001) and this observarion was most prominently seen in VIA (Fig. 3).

Similarily, in non-mastocytic patients undergoing VIA, urticaria or flushing as symptoms of anaphylaxis were present less often than if anaphylaxis was triggered by other elicitors (67.9% vs 70.1% respectively, p = 0.048). Moreover, in this specific subgroup of patients (i.e. non-mastocytic and at the same time lacking urticaria or flushing) VIA was significantly more frequently severe (52.9% in VIA vs. 47%, p < 0.001% in non-VIA).

After performing a factorial logistic regression modelling we confirmed the significant interaction effect between the presence of skin symptoms and the trigger (VIA) on the severity of anaphylaxis (p < 0.001). To recapitulate, non-mastocytic patients presenting without urticaria or flushing tended to have more severe anaphylaxis when it was triggered by insects, but not other elicitors of anaphylaxis (Fig. 3C, and Tab. S ??).

## Absence of skin symptoms correlates with BST levels and increases the risk of severe anaphylaxis specifically in IVA

Following the above-mentioned observation, we investigated the association of skin symptoms with the tryptase levels in non-masctoscytic patients. For this model, we excluded the cases with known mastocytosis and with BST above 11.5 ng/ml, potentially indicating non-diagnosed mastocytosis. Similarily, 1) tryptase levels correlated with the severity of anaphylaxis, 2) were higher in VIA patients, and 3) the effect was more prominently visible in VIA (p = 0.006). We did not observe this effect in the non-VIA group (Fig. 3D).

## Sub-elevated baseline serum tryptase and concomitant cardiovascular conditions increase the risk of severe VIA.

We evaluated potential cofactors increasing the risk of severe IVA. The factor most prominently associated with an increased risk of severe anaphylaxis was mastocytosis (Fig. 4), and it increased the risk of: 1) cardiac arrest and 2) loss of consciousness in patients undergoing VIA significantly more than in patients undergoing anaphylaxis due to other triggers (Fig. S8A and Fig. 4C).

In line with the above, BST levels also correlated with the severity of anaphylaxis (on the Ring and Messmer scale) and, most importantly, sub-elevated BST was more prominently increasing the risk of severe anaphylaxis in VIA than in non-VIA (Fig. 2D and Fig. 4B).

Concomitant cardiovascular diseases were more prevalent in VIA than in non-VIA cases (24.7% vs. 18.2%) and were associated with a higher risk of severe anaphylaxis when elicited by insects but were irrelevant in non-VIA cases (Fig. 4). Interestingly, BST values were increased in patients with concomitant cardiovasular diseases, irrespectively of the reaction severity (Fig. S9).

## Other cofactors of severe reactions (potentially could be shifted to th supplement)

Severe reactions of VIA were more prevalent in patients above 22 years of age, and in VIA cases vs. other elicitors (Fig. S10D). There were no differences in severity of reactions elicited by yellow-jackets and other insect species (p = 0.4128). .

The effect of using ACE-I (as well as beta-blockers) on the risk of severe anaphylaxis could not be independently measured from the coexisting cardiovascular pathologies. ACE-I use was, however, more often associated with cardiac arrests in all anaphylaxis cases (5.8% vs. 1.9%, p < 0.001) and there were no differences between VIA and non-VIA (Fig. 4C). Beta-blocker use was generally associated with higher severity of anaphylaxis and with the onset of cardiovascular symptoms (cardiac arrest, chest pain), but showed no difference between groups p = 0.199). Surprisingly, arrhythmia was more frequently reported in patients with VIA and concomitant beta-blockers (Fig. 4C).

## Nearly one-third of VIA patients experience repeated reactions

In general 28.6% of patients with insect allergy had experienced venom anaphylaxis in the past. If the reaction was elicited by other elcitors previous reactions were more frequently seen (35.7%, p < 0.001). We observed 227 patients with two documented reactions in our registry. Out of these 59 (26%) had insect elicited anaphylaxis and in 6 (10.2%) the following reaction was more severe than before. In 43 (72.9%) cases the reaction was similar in severity.

## Therapy: VIA recived adrenaline less often than non-VIA

Patients who underwent VIA significantly less often received adrenaline treatment than in other anaphylaxis cases (26.9% vs 34.6%, p < 0.001). After adjusting both groups for similar age, sex and severity distribution - the difference in adrenaline use was still significant irrespective of the administration route (p < 0.001, Fig 5).

Having a history of anaphylaxis also infuenced the therapy of a current episode. Adrenaline as a first-line treatment was given less often in VIA cases when compared to other cases **if patients did not report the previous history of anaphylaxis** (p < 0.001), but in patients who reported previous reactions, there was no difference in adrenaline therapy (p = 0.874, Suppl. Fig. 11). Similarly, there were no differences in adrenaline use between VIA and non-VIA when severe reactions were taken into consideration (p = 0.073). However, when we restricted the analysis to mild anaphylaxis cases — non-VIA patients received adrenaline more frequently than VIA (p < 0.001).

Patients with VIA received corticosteroids and antihistamines significantly more frequently than patients with anaphylaxis to other elicitors. On the other hand, adrenaline, beta-2 mimetics, and oxygen were given more often in non-VIA.

We discovered clusters of symptoms and therapy modes in VIA patients (association measured using phi coefficient). Cardiovascular symptoms (cardiac arrest, hypotension, loss of consciousness) and urticaria, were treated more similarly than respiratory or gastrointestinal symptoms (Fig. 5B). The treatment of these symptoms consisted of adrenaline autoinjector (AAI) use, i.v. adrenaline in multiple doses, 100% oxygen inhalation, an initial dose of antihistamines, and inhaled β-2 agonists. Corticosteroids, i.v. volume replacement and i.v. β-2 agonists formed another therapy mode. The most prominent difference in the therapy of VIA vs. non-VIA were regarging the inhaled beta2-agonists and antihistamines (Fig. 5B).

## Hymenoptera anaphylaxis is a seasonal disease (may be moved to supplement).

Insect venom elicited anaphylaxis in contrast to other elicitors showed a significant seasonal fluctuation and was most frequently reported from May to October. Their proportion of VIA to anaphylaxis cases elicited by other triggers during the summer seasons reached 60% and was as below 1% of cases during winter. Nevertheless, 116 cases of VIA (bee – *Apis mellifera* in spring; yellow jacket – *Vespula spp.* in autumn) were triggered in March, April, and November. Yellow-jacket was the most prominent VIA-causing insect followed by bees. The VIA-causing insects differed in European countries with hornets (*Vespa crabro*) being more prominent in southern Europe.

Outdoor physical exercise (e.g., jogging in the park) was more often associated with VIA than other triggers of anaphylaxis (p < 0.001). However, it was not associated with the severity of a reaction in these patients. (p = 0.436).

# Discussion

In this study, we identified distinctive clinical symptom-profile, and treatment patterns of venom induced anaphlaxis. The data unravel phenotypes of VIA, which may contribute to the development of tools incorporating clinical data for predicting the severity of future episodes of anaphylaxis.

VIA was more often associated with cardiovascular symptoms than non-VIA. Previous studies suggest [9,14,15] an essential link between the cardiovascular system and insect sting hypersensitivity. VIA has been associated with Kounis syndrome (coronary arterial spasm induced by the release of mast cell mediators [16,17]) and cardiac arrhythmias usually occurring in patients with preexisting heart disease [18].

The rate of concomitant cardiovascular diseases was higher in VIA than non-VIA; we observed them be an essential cofactor increasing the risk of a severe reaction **if insects elicited the anaphylaxis**. This association was not significant in anaphylaxis elicited by other triggers. Notably, cardiac arrest occurred more frequently in patients with the elevated BST (> 8 ng/ml), especially in VIA. Nevertheless, the pathomechanism promoting cardiovascular symptoms in VIA requires further investigation.

Of note, cardiovascular symptoms like hypotension, collapse, or cardiac arrest grade higher on the Ring and Messmer scale than skin or gastrointestinal symptoms. Since VIA predisposes to cardiovascular symptoms, it is likely to be associated with more severe anaphylaxis.

Importantly, the absence of skin symptoms was associated with more severe VIA, which was also true after we excluded patients with a known diagnosis of mastocytosis. Subsequently, we correlated the severity of anaphylaxis with BST levels and identified an interaction between the absence of skin symptoms and VIA using generalized linear regression.

Our findings indicate that patients with BST of over 8 ng/ml are prone to severe anaphylaxis to insect venom. Patients with normal BST in the range of 8-11.4 ng/ml may have indolent systemic mastocytosis or concomitant undiagnosed mast cell activation syndrome (MCAS) [19]. Zanotti et al. identified mast cell disorders in 17 out of 22 patients with VIA lacking skin symptoms [20] and concluded that patients with BST of 7.95 ng/ml and VIA should undergo extensive diagnostic procedures.

Based on our and previous findings [20–22] we propose to perform a peripheral blood KIT D816V mutation test in cases of BST of above 8 ng/ml and with a history of anaphylaxis presenting without urticaria or flushing.

Regarding the factors increasing the risk of VIA - older patients experienced VIA more frequently. Young patients mainly suffer from food-induced anaphylaxis [5]. One of the limitations of our registry is the fact that we can only compare cases of anaphylaxis and due to the lack of healthy cohort — cannot draw conclusions on the frequency of a particular type of anaphylaxis in the population.

Emergency room (ER) admission data indicate that the frequency of insect stings hypersensitivity reactions in children is comparable to food hypersensitivity reactions (12-15% of cases of hypersensitivity reactions admitted to the ER), but pediatric anaphylaxis is triggered significantly more often by food elicitors (56% of food hypersensitivity cases vs. 5.3% of sting cases seen in the ER) [23]. Senior patients, on the other hand, suffer from drug-related hypersensitivity more often than insect sting hypersensitivity [24]. Similarly, we saw less VIA in patients with concomitant atopic diseases, as these patients more often present with food anaphylaxis [25].

The influence of cardiovascular medication could not be isolated from the effect of concomitant cardiovascular conditions; therefore, we could not state if ACE-I and beta-blockers increased the severity of anaphylaxis. We did observe that there were no significant differences between VIA and non-VIA cases regarding the symptoms and severity of an episode with concomitant use of ACE-I or beta-blockers.

Cases of VIA had been treated with adrenaline less often than the age- sex- and severity-matched cases of non-VIA. Moreover, administration of adrenaline did not depend on the trigger if the patient experienced anaphylaxis previously, but was significantly less often used if the patient experienced their first episode of VIA. The difference between groups was prominent for milder cases of anaphylaxis. The reason for this observation is unclear. To our knowledge, this is the only data on the comparative adrenaline usage in a case-controlled group of VIA vs. non-VIA.

Nevertheless, international guidelines of anaphylaxis state that adrenaline (i.m.) is the first-line agent in all diagnosed cases of anaphylaxis [26]. Clinicians should not undermine the less severe VIA cases and treat them with adrenaline accordingly.

Although there are no absolute contraindications for using adrenaline in anaphylaxis, one potential scenario where clinicians tend to be reluctant to using adrenaline is hypersensitivity reaction with high blood pressure with tachycardia which might be present at the initial phase of VIA, due to a psychologic reflex. In theory, these less severe cases of VIA might exhibit some form of stress-related blood pressure increase, but we lack data to confirm or discard this theory.

Based on our findings, insects are the most probable anaphylaxis elicitor in Europe during Summer-season, with VIA cases extending from early Spring to the end of Autumn. Detailed information on the seasonality of insect-elicited hypersensitivity reactions is scarce [27]. The activity of *Vespula germanica* depends on the climate, and in invaded regions (e.i. Australia) it can even extend throughout the year [28]. The changing climate in Europe may influence the activity of Hymenoptera in this region in the upcoming years. However, in the period from 2007 - 2019, the perennial ratio of VIA to non-VIA cases has remained unchanged (data not shown).

Due to the design of the European Anaphylaxis Registry, our analysis was restricted only to cases of anaphylaxis. Milder hypersensitivity reactions, as well as healthy controls, are not included in the database. Although The European Anaphylaxis Registry is ideal for investigating anaphylaxis subtypes - it might give an incomplete picture of the populational distribution of hypersensitivity reactions and restricts us to only comparing various forms of anaphylaxis.

Nevertheless, because the European Anaphylaxis Registry has until now gathered over 12 000 cases of anaphylaxis - it was possible to perform a case-controlled analysis on a relatively large number of cases and investigate many aspects of VIA.

# Conclusion

Based on our results, VIA is a distinctive subtype of anaphylaxis, with a specific symptom profile and risk factors. VIA cases should undergo therapy according to the international management guidelines, and adrenaline should be given more often in VIA.

When evaluating the risk of future severe episodes - patients with BST over 8 ng/ml should undergo extensive diagnostic tests to exclude ISM or MCAS and should be provided with two adrenaline autoinjectors for acute self management.

# Acknowledgements

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# Figures

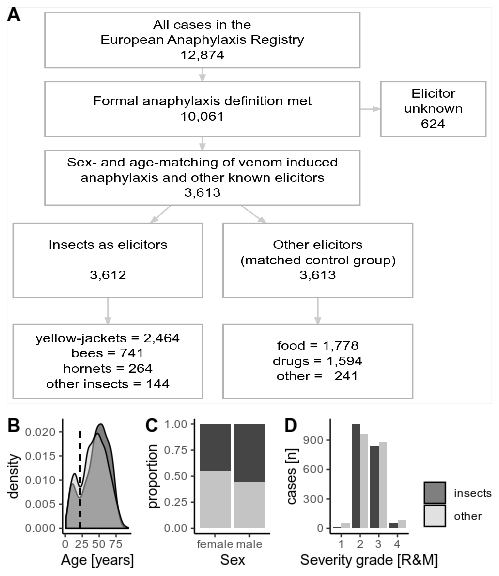


Figure 1: A) Flow-diagram illustrating the rationale for case inclusion and exclusion from the final analysis. B, C, D: Age, sex, and severity distribution was matched in cases in both groups to allow for comparable results between VIA and non-VIA cases. Two age-subsets of patients could be recognized based on the density plot of age (B).

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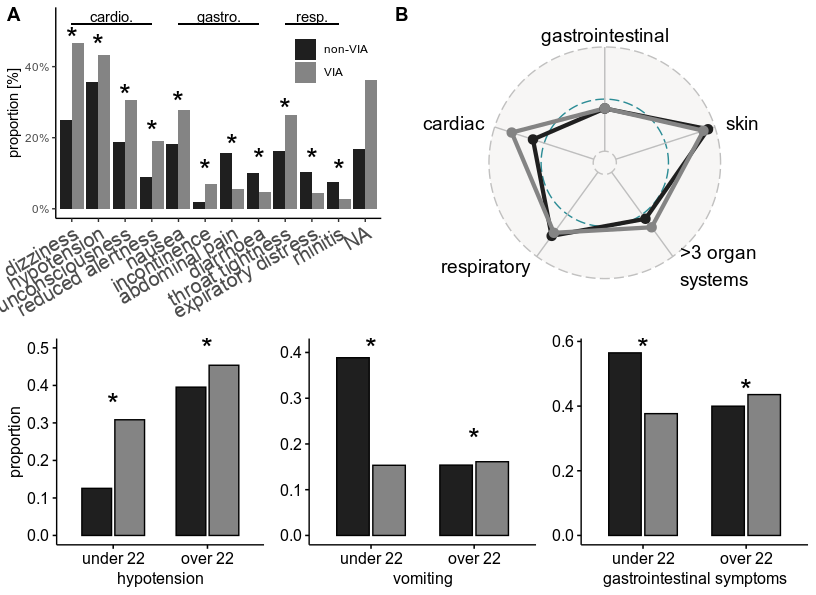


Figure 2: Symptoms of insect venom anaphylaxis (VIA) compared to other elicitors. A: Proportional presentation of specific reaction symptoms in VIA and non-VIA according to cardiovascular (cardio.), gastroenterologic (gastro.) and respirator (resp.) organ systems. B: High-level overview of involved organ systems and selected cofactors in the form of a radar plot. C: difference in symptoms of VIA among patients under 22 and over 22 years of age. \* denotes significant differences between groups. (other figure:Interaction effect of VIA and lack of skin symptoms (urticaria or flushing) on the severity of anaphylaxis. D: Baseline Serum Tryptase (BST) increases with the severity of anaphylaxis a lot more prominently in VIA.

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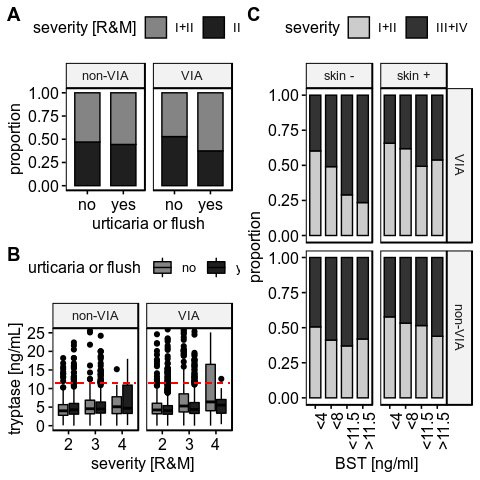


Figure 3: Lack of skin symptoms during anaphylaxis is associated with more severe IVA.

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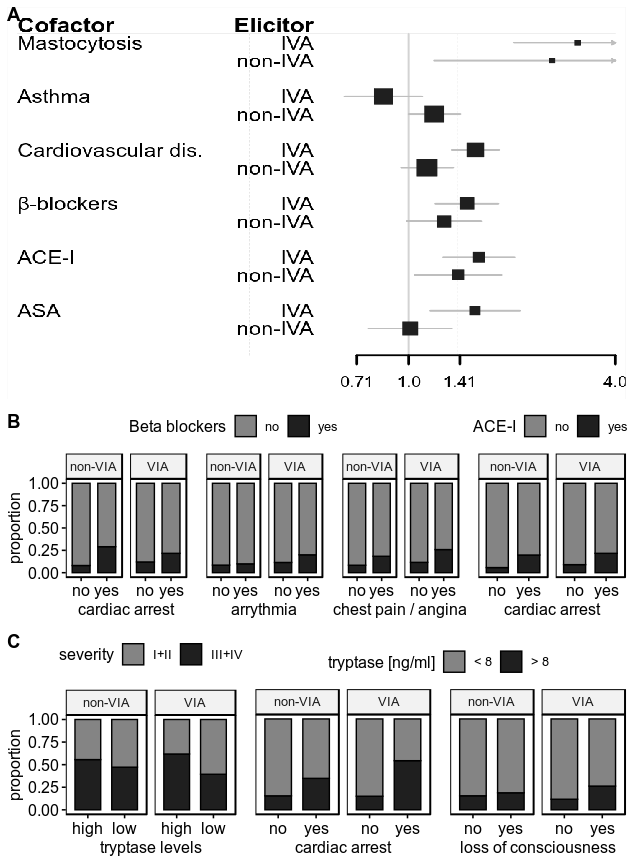


Figure 4: Cofactors of insect venom anaphylaxis. A: Odds ratios of eliciting severe anaphylaxis. B: Proportion of cases elicited by insects or other elicitors (upper panels) according to tryptase levels and cardiovascular symptoms.

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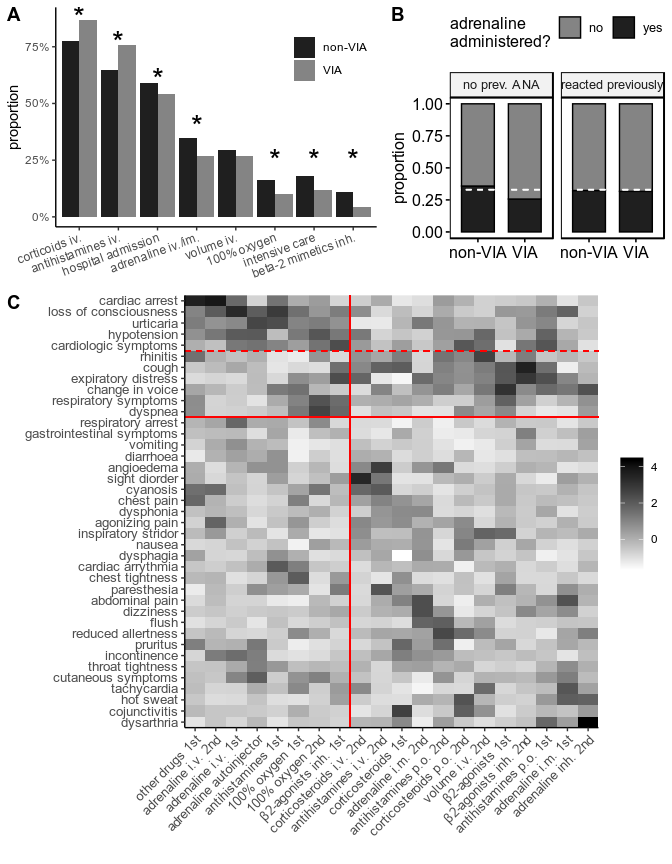


Figure 5: Therapy in patients with VIA compared to other elicitors, cases matched according to sex, age, and severity of a reaction. A: Proportional use of therapy measures in both anaphylaxis groups. B: C: Heatmap visualizing the association of symptoms and corresponding treatment - presented as a scaled correlation coefficient (phi). \* - p value < 0.05 after false discovery rate correction.

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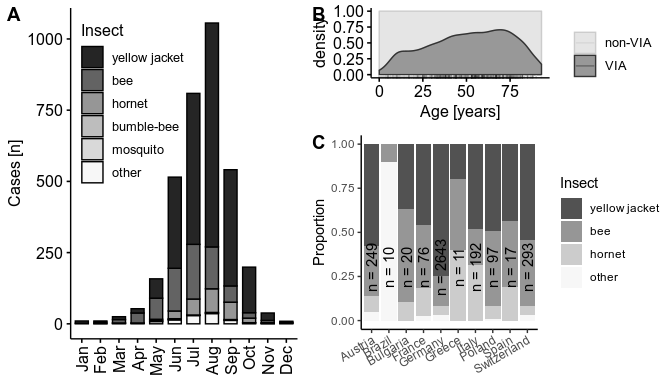


Figure 6: A: Proportion of anaphylaxis cases elicited by specific insects according to the month in which the reaction occurred. Less common insect species grouped as ‘other’. B: The density distribution of VIA cases to cases elicited by other triggers considering the patient’s age. C: Geographical differences in the most common elicitors of VIA. Countries which reported less than 10 VIA cases were not illustrated in this figure.

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# Supplementary Figures

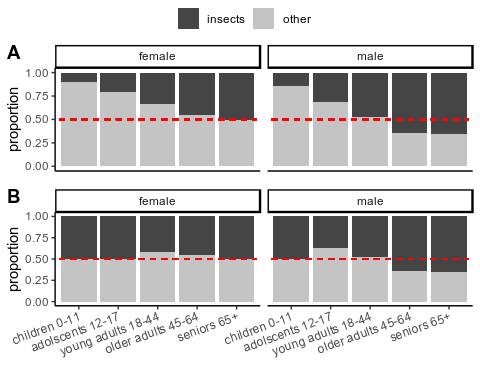


Figure 7: Results of matching the cohort according to sex and age in order to perform a case-controlled study. A: The original distribution of VIA and non-VIA cases according to age group and sex. B: The distribution of VIA and non-VIA after age and sex matching with the use of MatchIt package for R.

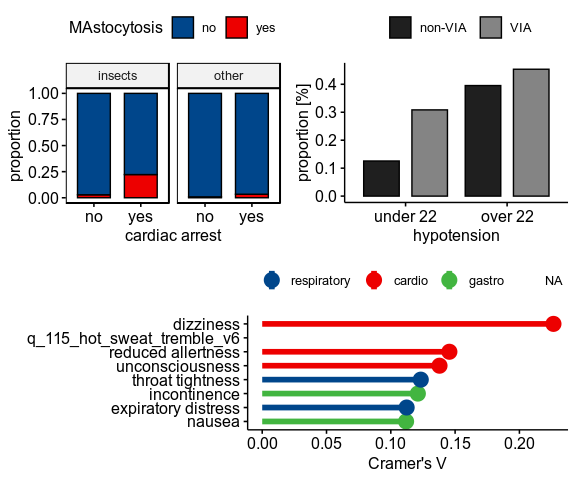


Figure 8: Symptoms of anaphylaxis. A: The association between cardiac arrest and concomitant mastocytosis in VIA and non-VIA. B: Hypotension frequency in two age groups of anaphylaxis. C: Crammer’s V as the measure of association between groups anaphylaxis (VIA vs. non-VIA).

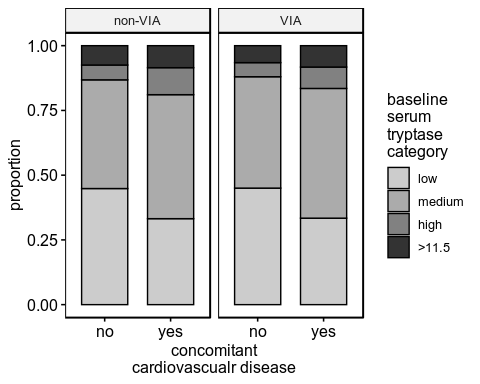


Figure 9: Tryptase levels in patients with concomitant cardiovascular diseases.

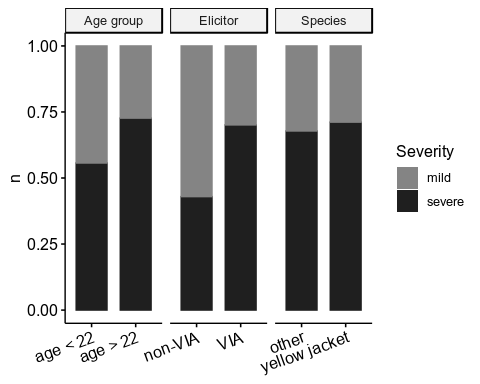


Figure 10: Severity of anaphylaxis in subgroups. The severity of patients with VIA in two age groups (left), according to elicitor type (center) and according to the responsible insect species (right)

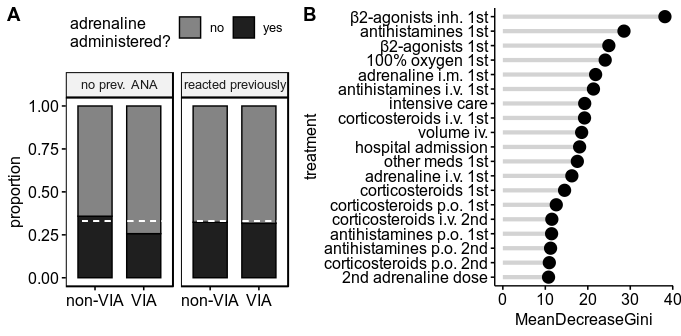


Figure 11: Therapy of anaphylaxis. A: Adrenaline use considering if patients had previous anaphylaxis. B: Variable impo

Dependent variable:

d\_severity\_rmr

groupingother

-0.202\*\*

(0.086)

d\_111\_urti\_flushyes

-0.625\*\*\*

(0.074)

groupingother:d\_111\_urti\_flushyes

0.542\*\*\*

(0.105)

Constant

0.123\*\*

(0.060)

Observations

6,901

Log Likelihood

-4,700.887

Akaike Inf. Crit.

9,409.773

Note:

*p<0.1;* ***p<0.05;*** p<0.01