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Epidemiology of sensitization to perennial aeroallergens in adults with severe asthma in Belgium. The BEIgE study

To the Editor,

The evaluation of the atopic (allergic) status is an integral part of asthma assessment.[1,2] There are no global guidelines on which allergens to test, and there are geographical variations.[3] The limited number of tests performed in clinical practice often complicates the management of patients with severe asthma (SA). By testing a panel of 43 perennial aeroallergens (PAAs) in 176 adult SA patients (Tables S1 and S2), this prospective study aimed at providing a detailed description of the epidemiology of sensitization to PAAs in SA. The individual PAAs were selected based on their relevance for Belgium, in concertation with academic experts. The analyses were performed in a central laboratory with a singleplex ImmunoCAP® assay using a Phadia 1000 analyzer (Thermo Scientific, serial number N10066) and commercially available ImmunoCAP® tests (ThermoFisher Scientific, Phadia AB, Uppsala, Sweden).

In our population (of whom 53% had a previously reported sensitization to a PAA), 68% tested positive for ≥1 PAA, 43% for ≥4, and 13% for >10 PAAs (Figure 1A). A higher number of prospective positive tests was associated with increased total serum IgE levels, reaching an 18-fold increase in patients with >10 positive tests versus nonpositive ($p < .0001$, Figure 1B). The most prevalent sensitizations were to the three house dust mites (HDMs) *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and *Dermatophagoides microceras*, and to *Aspergillus fumigatus*, *Staphylococcus aureus* Toxic Shock Syndrome Toxin (TSST), and *Candida albicans*, using two different sIgE cutoff levels (Figure 1C). Thus, this study provides evidence that the number of sensitizations to PAAs is underestimated in SA patients, being in line with previous data.[4]

Strikingly, our data indicate a high prevalence of sensitization to *S. aureus* toxins,[5] especially to TSST. The prevalence ranking in patients previously considered non-sensitized to PAAs but with at least one positive test in the prospective laboratory results, highlights the interest of evaluating sensitizations to these PAAs in patients suffering from severe asthma (Table S3).

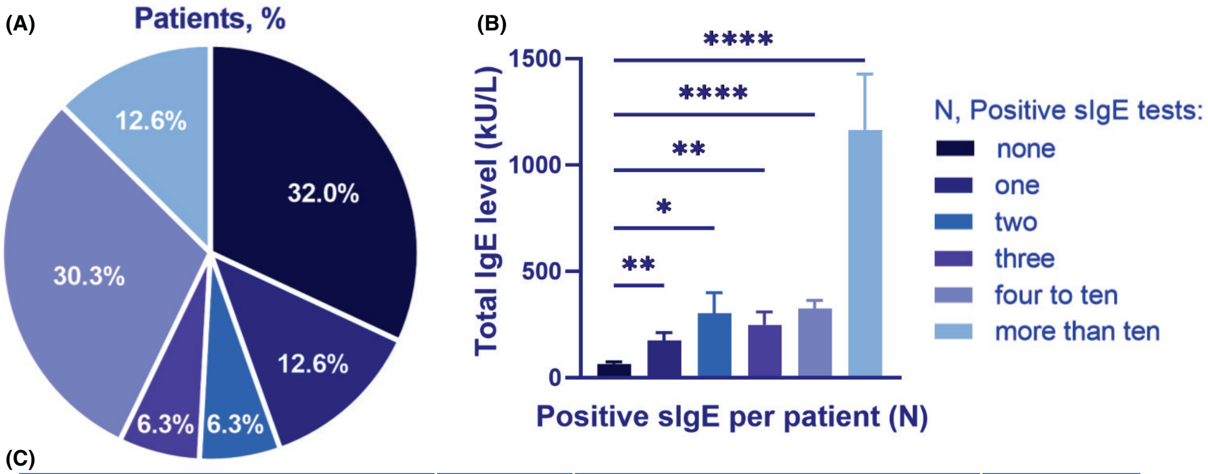
Interestingly, patients living in an urban area had overall a higher mean (±SEM) number of prospective positive tests compared to those living in a rural area (5.2 ± 0.6 vs 3.3 ± 0.4 tests, respectively, $p < .05$; Figure S1A), as well as an increase in total serum IgE (Figure S1B), a difference in the level of some sIgE (Figure S1C) and in the ranking of the most prevalent sensitizations (Figure S1D), despite similar clinical characteristics (not shown).

We also compared the ranking of sensitizations between patients with early versus adult-onset asthma (<18 years of age vs ≥18, respectively),[6] the latter representing the majority of patients included in this study (68.9%, mean ± SEM; age of onset 30.3 ± 1.5 years, Table S1). We found a marked difference in sensitization profiles between both groups (Table S3). There was a high prevalence of sensitization to 10 PAAs in patients with early onset asthma ($n = 52$); each of these 10 PAAs were positive in at least 25% of this population, whereas the prevalence did not exceed 25% in patients with adult-onset asthma ($n = 115$). The four most prevalent sensitizations were to the 4 HDMs in patients with early onset asthma, in contrast to *S. aureus*-TSST, *D. pteronyssinus*, *A. fumigatus*, and *C. albicans* in adult-onset asthma (Table S3).

We propose a diagnostic workup guideline (Table 1) to select and prioritize specific IgEs for testing in daily practice in countries with a PAA profile comparable to Belgium. We suggest omitting *D. farinae* and *D. microceras* given the redundancy (all patients sensitized to *D. farinae* and *D. microceras* were also sensitized to *D. pteronyssinus*). No other redundant tests were identified in the PAA test panel.

Testing for sensitizations to PAAs “beyond the usual suspects” should be considered by physicians managing patients with SA. In particular, *S. aureus* toxins should be added to the test panels for patients with SA, especially in those previously considered as “non-atopic.”

FIGURE 1 Characterization of sensitizations to perennial aeroallergens (PAAs) in the overall population of severe asthmatic (SA) patients (described in Table S1). (A) Percentage of patients with positive sIgE results (prevalence, %). (B) Prevalence of sensitizations to PAAs (%) and related serum total IgE levels. Data are represented as mean ± SEM. *$p < .05$, **$p < .01$, and ****$p < .0001$ versus 0 PAA (none), using the Kruskal–Wallis test and post hoc Dunn's test. (A and B) Sensitization is defined by CAP ≥0.35 kU/L. (C) List of PAAs by prevalence (%) and corresponding ranking, with sensitization defined by CAP ≥0.35 kU/L (*left*) or ≥0.1 kU/L (*right*).



(C)

Allergen species (name)	All patients, % (ranking) CAP ≥ 0.35 kU/L	Allergen species (name)	All patients, % (ranking) CAP ≥ 0.1 kU/L
Dermatophagoides pteronyssinus (d1)	29.9 (1)	*Dermatophagoides pteronyssinus* (d1)	46.6 (1)
Dermatophagoides farinae (d2)	28.0 (2)	*Dermatophagoides microceras* (d3)	41.4 (2)
Dermatophagoides microceras (d3)	26.4 (3)	*Staphylococcus aureus* TSST (m226)	40.5 (3)
Aspergillus fumigatus (m3)	24.7 (4)	*Dermatophagoides farinae* (d2)	40.0 (4)
Staphylococcus aureus TSST (m226)	21.4 (5)	*Aspergillus fumigatus* (m3)	36.5 (5)
Candida albicans (m5)	20.0 (6)	*Candida albicans* (m5)	35.9 (6)
Euroglyphus maynei (d74)	18.9 (7)	*Bombyx mori*, Moth (i8)	32.8 (7)
Cat dander (e1)	17.2 (8)	*Acarus siro* (d70)	27.4 (8)
Dog dander (e5)	17.2 (8)	*Glycyphagus domesticus* (d73)	27.2 (9)
Corylus avellana, common hazel (f17)	16.1 (10)	*Staphylococcus aureus* enterotoxin B (m81)	26.8 (10)
Blomia tropicalis (d201)	15.5 (11)	*Euroglyphus maynei* (d74)	25.7 (11)
Acarus siro (d70)	15.4 (12)	*Tyrophagus putrescentiae* (d72)	25.7 (11)
Tyrophagus putrescentiae (d72)	14.9 (13)	*Staphylococcus aureus* enterotoxin C (m223)	25.4 (13)
Bombyx mori, Moth (i8)	13.7 (14)	*Blomia tropicalis* (d201)	24.7 (14)
Lepidoglyphus destructor (d71)	13.1 (15)	*Lepidoglyphus destructor* (d71)	24.6 (15)
Trichophyton rubrum (m205)	12.2 (16)	Cockroach (i6)	24.1 (16)
Glycyphagus domesticus (d73)	11.6 (17)	Cat dander (e1)	23.6 (17)
Penicillium chrysogenum (m1)	11.0 (18)	*Staphylococcus aureus* enterotoxin A (m80)	23.5 (18)
Aspergillus niger (m207)	9.9 (19)	Dog dander (e5)	23.0 (19)
Staphylococcus aureus enterotoxin C (m223)	9.8 (20)	*Penicillium chrysogenum* (m1)	22.0 (20)
Staphylococcus aureus enterotoxin B (m81)	9.5 (21)	*Trichophyton rubrum* (m205)	21.5 (21)
Cockroach (i6)	8.6 (22)	*Corylus avellana*, common hazel (f17)	21.4 (22)
Staphylococcus aureus enterotoxin A (m80)	7.6 (23)	*Coleopterum* (i76)	20.3 (23)
Aspergillus flavus (m228)	7.6 (23)	*Aspergillus niger* (m207)	17.4 (24)
Arachis hypogaea, peanut (f13)	6.9 (25)	*Arachis hypogaea*, peanut (f13)	16.8 (25)
Helminthosporium halodes (m8)	4.8 (26)	Mouse epithelium (e71)	15.4 (26)
Aureobasidium pullulans (m12)	4.6 (27)	*Aspergillus flavus* (m228)	14.5 (27)
Alternaria alternata (m6)	4.2 (28)	*Aureobasidium pullulans* (m12)	12.7 (28)
Coleopterum (i76)	4.0 (29)	*Helminthosporium halodes* (m8)	11.3 (29)
Mouse epithelium (e71)	4.0 (29)	Ficus (k81)	10.9 (30)
Cladosporium herbarum (m2)	3.5 (31)	*Alternaria alternata* (m6)	10.8 (31)
Guinea pig epithelium (e6)	2.9 (32)	*Cladosporium herbarum* (m2)	7.6 (32)
Hamster epithelium (e84)	2.9 (32)	*Mucor racemosus* (m4)	7.0 (33)
Rhizopus nigricans (m11)	2.3 (34)	*Rhizopus nigricans* (m11)	6.9 (34)
Trichoderma viride (m15)	2.3 (34)	*Trichoderma viride* (m15)	6.3 (35)
Chaetomium globosum (m208)	1.7 (36)	Guinea pig epithelium (e6)	6.3 (35)
Rat epithelium serum and urine (e87)	1.7 (36)	Rat epithelium serum and urine (e87)	6.3 (35)
Ficus (k81)	1.7 (36)	*Chaetomium globosum* (m208)	5.8 (38)
Mealworm (o211)	1.2 (39)	Hamster epithelium (e84)	5.7 (39)
Mucor racemosus (m4)	1.2 (39)	*Penicillium frequentans* (m209)	5.2 (40)
Penicillium frequentans (m209)	1.2 (39)	Latex (k82)	2.9 (41)
Formaldehyde (k80)	0.0 (42)	Mealworm (o211)	2.4 (42)
Latex (k82)	0.0 (43)	Formaldehyde (k80)	0.0 (43)

TABLE 1 Proposed diagnostic workup of patients with severe asthma.

	All patients		All patients
	% (ranking)		% (ranking)
Allergen species (name)	CAP ≥0.35 kU/L	Allergen species (name)	CAP ≥0.1 kU/L
Dermatophagoides pteronyssinus (d1)	29.9 (1)	*Dermatophagoides pteronyssinus* (d1)	46.6 (1)
Aspergillus fumigatus (m3)	24.7 (2)	*Staphylococcus aureus* TSST (m226)	40.5 (2)
Staphylococcus aureus TSST (m226)	21.4 (3)	*Aspergillus fumigatus* (m3)	36.5 (3)
Candida albicans (m5)	20.0 (4)	*Candida albicans* (m5)	35.9 (4)
Euroglyphus maynei (d74)	18.9 (5)	*Bombyx mori*, Moth (i8)	32.8 (5)
Cat dander (e1)	17.2 (6)[a]	*Acarus siro* (d70)	27.4 (6)
Dog dander (e5)	17.2 (6)[a]	*Glycyphagus domesticus* (d73)	27.2 (7)
Corylus avellana, common hazel (f17)	16.1 (8)	*Staphylococcus aureus* enterotoxin B (m81)	26.8 (8)
Blomia tropicalis (d201)	15.5 (9)	*Euroglyphus maynei* (d74)	25.7 (9)
Acarus siro (d70)	15.4 (10)	*Tyrophagus putrescentiae* (d72)	25.7 (9)
Tyrophagus putrescentiae (d72)	14.9 (11)	*Staphylococcus aureus* enterotoxin C (m223)	25.4 (11)
Bombyx mori, Moth (i8)	13.7 (12)	*Blomia tropicalis* (d201)	24.7 (12)
Lepidoglyphus destructor (d71)	13.1 (13)		

Note: Prevalence of sensitizations (%) to PAAs and ranking in patients with SA in the overall population ($N = 175$ patients) after exclusion of the tests that can be regarded as redundant. Ranking is provided within parentheses. Sensitization is defined by CAP ≥0.35 kU/L (*left*) or CAP ≥0.1 kU/L (*right*). For each PAA, allergen class is provided in Table S2.

[a] The PAAs for which a choice should be made based on clinical context.

AUTHOR CONTRIBUTIONS

Jan Van Schoor, Sandra Gurdain, and Mieke Jansen are accountable for study concept and design, Jan Van Schoor and Sandra Gurdain for data collection, Eléonore Maury for data analysis, and Eléonore Maury and Jan Van Schoor for the interpretation of data. Eléonore Maury and Jan Van Schoor drafted the article. Florence Schleich, Claus Bachert, Shane Hanon, and Olivier Michel performed critical revision of the article for important intellectual content. Jan Van Schoor supervised, initiated, and guided the entire project. All authors gave final approval of the version to be published.

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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REFERENCES

1. Akar-Ghibril N, Casale T, Custovic A, Phipatanakul W. Allergic endotypes and phenotypes of asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):429-440.
2. Global Initiative for Asthma. https://ginasthma.org
3. Heinzerling L, Mari A, Bergmann KC, et al. The skin prick test—European standards. *Clin Transl Allergy*. 2013;3(1):3.
4. Koschel D, Mailänder C, Schwab Sauerbeck I, Schreiber J. Non-allergic severe asthma: is it really always non-allergic? The IDENTIFY project. *Allergy Asthma Clin Immunol*. 2020;16(1):92.
5. Bachert C, Humbert M, Hanania NA, et al. *Staphylococcus aureus* and its IgE-inducing enterotoxins in asthma: current knowledge. *Eur Respir J*. 2020;55(4):1901592.
6. Quirce S, Heffler E, Nenasheva N, et al. Revisiting late-onset asthma: clinical characteristics and association with allergy. *J Asthma Allergy*. 2020;13:743-752.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Social media to monitor prevalent diseases: Hay fever and Twitter activity in Germany

To the Editor,

Allergic rhinitis (AR), also known as hay fever, is the most common allergic disease worldwide, affecting up to 30% of the global population.[1] The analysis of publicly available, population-based data can be beneficial for novel insights and monitoring of the disease burden in populations.[2] One source for these data is social media, which are gaining increased interest in medicine and public health. Twitter is among the most popular social media sites in Germany, with a market share of about 20%.[3] Tweet counts were shown to correlate with local pollen counts in some countries.[4] The aim of our study was to provide insight into the German AR landscape on Twitter and to identify influential regional climate factors for the future development of tailored awareness and prevention campaigns.

A total of 43,965 tweets in German language containing the keyword "*heuschnupfen*" (hay fever) from 2018 to 2021 were found by querying the Twitter Academic API using the query string "*heuschnupfen lang:de*." The keyword is searched against the tokenized tweet body (i.e., split by punctuation or spaces) and includes hashtags. The year range was chosen based on the available pollen data in Bavaria, which were kindly provided by the Center Allergy and Environment (ZAUM) and used as proxies for pollen counts in Germany. The tweets originated from the German-speaking countries such as Germany, Austria, and Switzerland; however,