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1. Aktuelle Fachinformation TREMFYA®.

2. Reich K et al. Lancet. 2019;394(10201):831-839.

3. Griffiths CEM et al. Poster Presentation Coastal Dermatology Symposium 2020, October 15-16th.

4. Mease P et al. The Lancet 2020; [https://doi.org/10.1016/S0140-6736\(20\)30263-4](https://doi.org/10.1016/S0140-6736(20)30263-4) (Supplementary)

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Sensitization rates to common inhaled allergens in Germany – increase and change patterns over the last 20 years

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Summary

Background: Sensitization rates to aeroallergens are rising worldwide. The prevalence is increasing, especially in Western countries. We aimed to investigate (1) sensitization rates and (2) cross-sensitization patterns in skin prick tests (SPTs) for the most relevant inhaled allergens in central Germany over 20 years, adjusted for regional pollen counts.

Patients and Methods: This monocentric study evaluated SPTs for tree pollen, grass pollen and house dust mites (HDMs) in 4,315 patients (including children) with suspected airway allergies, from 1998–2017.

Results: Sensitization rates to almost all aeroallergens have increased significantly over time, without relevant changes in regional pollen counts. Current sensitization rates in all our symptomatic patients were highest for grass (55.3 %) and rye pollen (59.6 %), with most pronounced increases in HDM sensitization over time (from 37.8 % to the current figure of 50.1 %). However, a low but consistent proportion of tree-sensitized patients (3.6–7.8 %) showed isolated positive SPTs to alder and/or hazel pollen without sensitization to birch pollen.

Conclusions: We demonstrate a significant rise in the total number of sensitized patients as well as increases in cross-sensitization between closely related allergens. Individuals with unusual mono-sensitization profiles to common inhaled allergens should be studied in more detail, since these patients are currently excluded from clinical trials for allergen immunotherapy.

Introduction

Approximately 10–30 % of the global population suffers from allergic diseases, with considerable variation in different countries and geographical regions [1]. In Europe, the overall prevalence of airway allergies increased to 31 % in recent years. This has resulted in various negative consequences for affected individuals, including comorbid conditions such as bronchial asthma, impaired quality of life, and rising medical and socio-economic costs [2]. At the national level in Europe, prevalence rates of allergies to common aeroallergens reveal considerable geographic variation, underlining the probable influence of environmental factors such as regional pollen counts and climate change as well as nutrition, infections, and economic development [3, 4].

The German population was last investigated almost ten years ago, when 20 % of participants were found to suffer from at least one allergic disease [5]. Airway allergies are the most common allergic diseases in Germany. The lifetime prevalence of physician-diagnosed allergic rhinitis (AR) remained consistently high at 14.8 %, while for bronchial asthma it increased up to 8.6 % in adults. The prevalence of sensitization to aeroallergens in adults showed a significant increase from 29.8 % to 33.6 % between 1998 (Federal Health Survey 1998, BGS98) and the follow-up in 2008–2011 (German Health Interview and Examination Survey for Adults, DEGS1) [5–8]. In German children, the prevalence of serological sensitization to aeroallergens (specific immunoglobulin E [sIgE] to sxl-screen) was found to be 36.2 %, as shown in 2003–2006 during the initial survey of the KiGGS

study (Study on the Health of Children and Adolescents in Germany) [7]. The first follow-up survey (KiGGS wave 1, 2009–2012) confirmed the earlier results, with a prevalence of AR at 12.6 % and asthma at 6.3 % [8].

The most frequent allergic reaction is an IgE-mediated immediate-type allergy. Clinical manifestations include allergic rhinoconjunctivitis, asthma, food allergy, and anaphylaxis. Since skin prick tests (SPTs) are the gold standard for diagnosis of IgE-mediated inhaled allergies; they should be a prerequisite for the exact description of prevalence, with later tests for clinical relevance based on nasal provocation with the suspected allergen [9, 10]. A significant limitation in epidemiology is that most larger studies estimate lifetime prevalence based on interviews regarding allergic symptoms, prescription data (e.g. anti-allergic medication), or patient self-reported and physician-diagnosed allergic diseases in their medical history. Only a few studies have used objective diagnostic instruments such as SPTs or analysis of sIgE in blood samples to investigate changes in prevalence of sensitization to inhaled allergens [11–14]. In addition, provocation tests for confirmation of clinical relevance and exclusion of clinically silent sensitization are rarely performed in these studies, although the current guidelines recommend them for correct diagnosis of allergic rhinitis [15]. Another important bias in studies of prevalence rates may be caused by changing levels of pollen exposure in different regions [16]. Various longitudinal studies precisely describe the relationship between the level of pollen exposure and the severity of allergic symptoms and/or the amount of disease control medication required [17–19]. Since pollen counts vary significantly from one season to the next over long periods due to environmental and climatic changes, incorporating these data is of the utmost importance for high quality studies [16]. We therefore carried out a retrospective analysis of data from a large patient cohort of symptomatic SPT patients in central Germany. Changes of sensitization rates and cross-allergy patterns regarding the most relevant aeroallergens over the past 20 years were investigated in detail, including an analysis of regional pollen levels.

Patients and methods

Recording pollen levels

Pollen levels were recorded at four pollen-monitoring stations (PMSts) in Göttingen and its surrounding stations in Jena, Bad Lippspringe, and Fulda (all located in central Germany, maximum distance of 215 km between these PMSts). Pollen was collected with 7-day volumetric spore traps placed at rooftop level. Pollen grains were trapped on an adhesive medium, and daily slides were prepared and analyzed under a light microscope. Pollen types *Alnus* (alder), *Betula* (birch),

Corylus (hazel), and *Poaceae* (grass family, including rye [*Secale*]) were determined. Average daily pollen concentrations were reported in pollen grains per cubic meter. Daily pollen concentrations from the PMSts were averaged for each of the four observed taxa and cumulative annual totals were calculated.

Patients and clinical data evaluation

Results of SPTs of consecutive symptomatic patients in our clinic were retrospectively evaluated from 1998–2017. Patients were divided into three four-year intervals: 1998–2001 ($n = 2093$ patients), 2006–2009 ($n = 1034$ patients), and 2014–2017 ($n = 1188$ patients). Overall, the patient group was comprised of 62.7 % women and 37.3 % men. During the four-year intervals, the gender proportions remained largely unchanged (62.2 % vs. 62.4 vs. 63.8 % women). The intervals were compared with respect to patient age, gender, reaction level in the SPT, and sensitization rates of the three major aeroallergen groups in Germany, including tree pollen of birch (*Betula*), alder (*Alnus*), and hazel (*Corylus*), as well as grass (*Poaceae*) pollen (a common mixture of pollen of different grass species without rye [*Secale*]) and rye pollen, and house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*). Sensitization patterns and shifts of mono-sensitization and cross-reactivity were also investigated within the major allergen groups over time. Therefore, only patients who received an SPT for all allergens within one of the three major allergen groups were included. Without molecular diagnostics it is impossible to make reliable statements on cross-sensitization. However, since multiple sensitizations to structurally related aeroallergen groups (tree pollen, grass pollen, house dust mites [HDMs]) are mainly due to cross-sensitization [20], this term is used here.

Skin prick test (SPT)

In the 20-year period considered here, the SPT as standard series (or series of atopy) was performed exclusively by only three experienced nurses in a standardized procedure according to the guidelines of the German Society for Allergy and Clinical Immunology (DGAKI, [21]). Investigator-dependent subjective variability was thus reduced to a minimum. A skin reaction with an average wheal diameter ≥ 2 mm was considered positive. At the time of implementation of SPT in the late 1990s, wheal reactions > 2 mm were regarded as positive [22, 23]. For epidemiologic studies, the interpretation of wheal diameter less than 3 mm as positive was explicitly recommended at that time [24]. Since these recommendations changed over time, we currently evaluate diameters ≥ 3 mm as positive [21]. For investigation of patients with strong reactions to SPT, we analyzed positive reactions with

≥ 6 mm diameter separately. Histamine dihydrochloride was employed as a positive control, and sodium chloride solution as a negative control. During these 20 years, standardized commercial extracts for all allergens were obtained exclusively from ALK Abelló (ALK-prick SQ, ALK Abelló, Hamburg, Germany) and Allergopharma (Reinbek, Germany). All SPT extracts of these common allergens were approved by the Paul Ehrlich Institute between 1985 and 1989. These approvals have remained unchanged over time and are still valid today. Thus, manufacturing and standardization procedures as well as quality management for batch-to-batch consistency remained unaltered during the whole study period.

Statistical analyses

Data were analyzed using the statistical analysis software SAS®, version 9.4 (SAS Institute, Cary, NC, USA) and the R statistical software package (version 3.4.4, <https://www.r-project.org/>, RRID:SCR_001905). Differences between multiple time intervals were tested for significance using the two-sided Cochrane-Armitage trend test. Each table contains information on the tests employed in the legend; results were regarded as significant for $p < 0.05$.

Results

Alnus (alder), *Betula* (birch), *Corylus* (hazel), and *Poaceae* (grass family, including rye [*Secale*]) pollen was collected during the three four-year intervals 1998–2001, 2006–2009, and 2014–2017 at regional pollen-monitoring stations (Figure 1). Comparison of the mean values of each annual pollen count over time revealed a slight increase in *Betula* and *Corylus* pollen levels without reaching significance, while the variation of all other pollen data did not differ during

the three intervals. We did not identify a consistent trend toward increasing or decreasing counts for any pollen analyzed here. Thus, any changes in prevalence rates of sensitization to aeroallergens cannot be attributed to temporary or consistent variation of local pollen counts. Regarding the patient characteristics of our study cohort over 20 years, female patients were always higher in number (62.7 %) than males, without relevant changes. Of note, our study population included children/adolescents as well as adults (Table 1). Children and young individuals (0–20 years of age) accounted for 12.5–16.4 % of our study population. Over the last 20 years, our patients grew older, and this change was consistent and significant (Table 1). We also observed a slight decrease in numbers of children and adolescents, and a significant decrease in younger adults (21–40 years of age) in favor of older adults and seniors.

We next focused on the prevalence of sensitization, and analyzed total and relative numbers of positive SPTs to the most important inhaled allergens (alder, hazel, birch, grass, and rye pollen), as well as *D. pteronyssinus* and *D. farinae* in the study intervals (Table 2). Grass and rye pollen extracts were used separately for skin tests, while the grass and rye pollen counts in Figure 1 are combined into one category, since differentiation of these closely related pollens is difficult with light microscopy. Sensitization rates of almost all aeroallergens increased significantly across the three intervals, with the sole exceptions of rye and alder, which remained unchanged. The highest sensitization rates were found for rye pollen and grass pollen. However, all pollen was found with comparably high positivity rates in our study population (50.3 %–59.6 % in the last interval). The initially lower sensitization rates to both HDMs increased most prominently over the study period (*D. pteronyssinus*: 37.8 % vs. 49.9 % vs. 50.1 %; $p < 0.0001$ / *D. farinae* 32.6 % vs. 43.9 % vs.

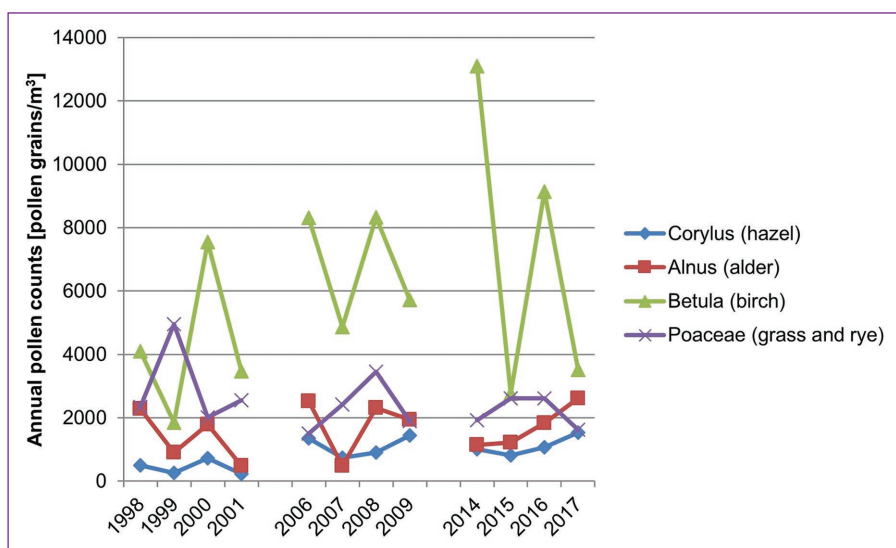


Figure 1 Annual pollen counts for the years 1998–2001, 2006–2009, and 2014–2017, for *Alnus* (alder), *Corylus* (hazel), *Betula* (birch), and *Poaceae* (the grass family including rye), recorded by four regional pollen-monitoring stations located around the study center.

Table 1 Age distribution in skin prick test patients during the study period displays a small, but relevant shift towards increased age of tested patients. The age distribution for every 10-year interval of patient ages are depicted with relative patient numbers from each 4-year cohort and total patient numbers in brackets. Significantly decreased proportions and significantly increased proportions over the study period are marked in bold (by two-sided Cochran-Armitage trend test). Two patients from the 1998–2001 cohort and one patient from the 2014–2017 cohort were missing data for age.

Patient age [years]	1998–2001 (n = 2,093)	2006–2009 (n = 1,034)	2014–2017 (n = 1,188)	p-value
00–10	5.0 % (104)	4.6 % (48)	2.7 % (32)	*0.0043
11–20	11.3 % (236)	11.8 % (122)	9.8 % (117)	0.3176
21–30	21.1 % (442)	14.2 % (147)	17.7 % (210)	*0.0136
31–40	18.9 % (395)	17.0 % (176)	15.2 % (180)	*0.0218
41–50	17.5 % (367)	20.1 % (208)	18.2 % (216)	0.5644
51–60	14.6 % (306)	16.2 % (167)	18.6 % (221)	*0.0120
61–70	8.8 % (184)	11.5 % (119)	12.0 % (142)	*0.0063
71–80	2.4 % (50)	4.2 % (43)	5.0 % (59)	*0.0001
81–90	0.3 % (6)	0.4 % (4)	0.8 % (10)	*0.0309
> 90	0.0 % (1)	0	0	–

46.4 %; $p < 0.0001$). In all intervals, sensitization to *D. pteronyssinus* was slightly more pronounced than to *D. farinae*, without reaching statistical significance (Table 2). We investigated time trends of strongly positive SPT reactions (defined here as wheal diameter ≥ 6 mm) relative to all positive SPT reactions, and calculated the relative percentages for the three 4-year intervals for every allergen. We also tested for significant changes over time with the two-sided Cochran-Armitage

trend test (data not shown). Significant increases in strong positive SPTs were observed for *D. pteronyssinus* ($p < 0.001$), *D. farinae* ($p < 0.01$), hazel pollen ($p < 0.001$), birch pollen ($p < 0.001$), and rye pollen ($p < 0.05$). For alder and grass pollen, identical trends over time were found, with no significant difference.

Finally, we analyzed mono- and cross-sensitization in three allergen groups: tree pollen, grass pollen and HDMs,

Table 2 Total number of skin prick tests, and relative numbers of positive results. The analysis comprised of the three intervals 1998–2001, 2006–2009 and 2014–2017 and contained five pollen taxa (alder, hazel, birch, grass, rye) and two house dust mite species (*D. pteronyssinus*, *D. farinae*). Significantly increased proportions over the study period are marked in bold (by two-sided Cochran-Armitage trend test).

Allergen	1998–2001		2006–2009		2014–2017		p-value
	Total number	Positive % (n)	Total number	Positive % (n)	Total number	Positive % (n)	
Alder pollen	761	56.1 (427)	334	49.1 (164)	432	52.5 (227)	0.1550
Hazel pollen	1116	42.5 (474)	419	46.1 (193)	579	50.3 (291)	*0.0021
Birch pollen	1008	44.1 (445)	407	54.1 (220)	571	52.9 (302)	*0.0003
Grass pollen	1011	51.1 (517)	410	67.3 (276)	571	55.3 (316)	*0.0216
Rye pollen	760	65.4 (497)	334	66.2 (221)	267	59.6 (159)	0.1450
<i>Dermatophagoides pteronyssinus</i>	876	37.8 (331)	375	49.9 (187)	519	50.1 (260)	* < 0.0001
<i>Dermatophagoides farinae</i>	937	32.6 (305)	380	43.9 (167)	521	46.4 (242)	* < 0.0001

Table 3 Mono- and cross-sensitization within taxonomic families *Betulaceae* (alder, hazel, birch), *Poaceae* (grass, rye), and within the *Dermatophagoides* species. The *Betulaceae* study group comprised 436 patients with positive SPT to at least one tree pollen out of 657 patients tested in 1998–2001, 201/315 patients in 2006–2009, and 255/414 in 2014–2017. The *Poaceae* cohort included 473 patients with positive SPT to at least one grass pollen out of 658 patients tested in 1998–2001, 242/315 patients in 2006–2009, and 170/248 in 2014–2017. The *Dermatophagoides* group (*D. pteronyssinus*, *D. farinae*) consisted of 352 patients with positive SPT to at least one house dust mite out of 874 patients tested in 1998–2001, 198/375 patients in 2006–2009, and 274/519 in 2014–2017.

Allergens			Patients [relative and total numbers]		
Alder	Hazel	Birch	1998–2001	2006–2009	2013–2017
+	–	–	1.6 % (7)	1.0 % (2)	0.8 % (2)
–	+	–	4.4 % (19)	2.5 % (5)	2.4 % (6)
–	–	+	5.7 % (25)	12.9 % (26)	8.2 % (21)
+	+	–	1.8 % (8)	0.5 % (1)	0.4 % (1)
+	–	+	4.6 % (20)	4.5 % (9)	1.2 % (3)
–	+	+	5.3 % (23)	5.0 % (10)	2.4 % (6)
+	+	+	76.6 % (334)	73.6 % (148)	84.7 % (216)
Grass	Rye				
+	–		7.6 % (36)	9.9 % (24)	11.2 % (19)
–	+		2.5 % (12)	2.1 % (5)	2.4 % (4)
+	+		89.9 % (425)	88.0 % (213)	86.5 % (147)
<i>D. pter.</i>	<i>D. far.</i>				
+	–		20.2 % (71)	16.7 % (33)	11.7 % (32)
–	+		6.5 % (23)	5.6 % (11)	5.1 % (14)
+	+		73.3 % (258)	77.8 % (154)	83.2 % (228)

Abbr.: *D. pter.*, *Dermatophagoides pteronyssinus*; *D. far.*, *Dermatophagoides farinae*.

in the years 1998–2017. Data are presented in Table 3 for the three intervals. Within the three major allergen groups, our patient population showed high cross-sensitization rates between related allergens (e.g. alder, birch, hazel) ranging from 83.2 % to 86.5 % in the most recent interval (Table 3). Interestingly, not every patient was found to be sensitized to all related allergens of one group (e.g., tree pollen). Of note, sensitization to alder and/or hazel pollen without a positive SPT to birch pollen was observed in 3.6–7.8 % of the tree-sensitized patients. Furthermore, mono-sensitization to rye pollen was determined in the grass-sensitized patients with 2.1–2.5 %, and mono-sensitization to *D. farinae* was found in 5.1–6.5 % in the HDM-sensitized patients. In line with our earlier results, we found significant increases in cross-sensitization rates in related allergen groups for tree pollen and HDMs. Cross-sensitization in patients to all three of birch, alder, and hazel pollen increased significantly from 76.6 % to 84.7 % over time ($p = 0.025$) (Table 3), and

sensitization rates to both *D. pteronyssinus* and *D. farinae* rose from 73.3 % to 83.2 % ($p = 0.003$) (Table 3). Cross-sensitization to both rye and grass pollen remained almost unchanged at high levels with 86.5 % to 89.9 %. In contrast to these findings of increased cross-sensitization rates within these groups, the percentage of mono-sensitized patients declined for most allergens.

Discussion

Although annual pollen counts in central Germany remained almost unaltered, climate change and air pollution over the last two decades may have prolonged exposure times and led to increased sensitization rates, even at largely stable pollen concentrations [25]. The gender and age of our patient population remained relatively homogeneous, with small but significant increases in age over time in tested patients. Several studies have shown different sensitization rates based on age

and sex [6, 26–29]. Since the patients at our university outpatient clinic were referred due to suspected allergic rhinitis or other type I allergic diseases, our sensitization rates are markedly higher than in population-based studies. Furthermore, some patients may have been sent to our clinic with more severe or more complex allergic diseases, although we cannot provide evidence in support of this hypothesis. Since sensitization rates are generally higher in children [7], and specifically increased in younger Germans than in adults [6], the large age range of our study cohort (which included children) may result in our sensitization rates being higher than those reported for population-based studies. The clinical relevance of sensitization to inhaled allergens is associated with allergen-specific wheal size in the SPT, as demonstrated in the large European dataset of SPTs in the GA²LEN study (Global Allergy and Asthma European Network) [30]. Our increasing relative amount of strongly positive SPTs may suggest an increasing number of clinically relevant sensitized patients. Of note, commercial SPT extracts from only two different manufacturers were used during these 20 years, and only three nurses applied the tests during the study period, thus ruling out significant bias for these parameters. Some minor variations cannot be completely excluded in a pharmaceutical product of natural origin, despite the manufacturers' elaborate efforts to ensure that all relevant allergens with intact epitopes are present in the SPT preparations and that there is batch-to-batch consistency. However, since we investigate time trends over 20 years in more than 4,000 patients, these effects should have a rather limited impact on our results.

Limited data based on SPT results are available in Germany for rates of sensitization to aeroallergens. We recently published results on increasing numbers of patients with SPTs positive for weeds in our region during the last 20 years [31]. In the population-based European skin prick test study I from the GA²LEN community (14 countries, 2000–2001), sensitization rates for Germany were 37.9 % for grass, 37.6 % for birch, 35.9 % for hazel, and 34.8 % for alder pollen [10]. Sensitization rates for HDMs were much lower (*D. pteronyssinus*: 23.5 %, *D. farinae*: 21.1 %). Since SPTs and *in vitro* tests for sIgE are widely comparable diagnostic tools, we would challenge epidemiologic studies based on serological diagnostics with our results [32, 33]. The latest estimate of prevalence for the German population dates back to 1998 (BGS98, 18–79-year-old individuals) and 2008–2011 (DEGS1, 18–79-year-old individuals). These studies showed an increase in sensitization rates (sx1-screen) from 29.8 % in 1998 to 33.6 % in 2008–2011. In German children (3–17 years old), the population-based KiGGS baseline survey from 2003–2006 revealed rates of sensitization in sx1-screens of 40.8 % [34].

Cross-reactions rather than co-sensitizations appear significantly more often within allergen groups of similar structure [20, 35]. This clinical effect is well known for

pollen from the taxonomic family *Betulaceae* (the birch family), the taxonomic family *Poaceae* (the grass family), and for the *Dermatophagoides* species [36]. Significant increases of cross-sensitization in our study cohort may be partly explained by the increased sensitization rates of birch and hazel pollen relative to all tested patients, as well as increases in positive SPTs to both HDMs over all intervals. Related allergens are even considered interchangeable from a regulatory perspective: the guideline on allergen products of the European Medicines Agency transfers data for efficacy, safety, and quality of a representative allergen extract to other extracts of the same allergen group (based on the concept of homologous groups) [37]. Based on cross-reactivity studies, birch was selected as a representative allergen in the *Betulaceae* group [36, 38]. Serological cross-sensitization of hazel and alder was shown in all individuals of a German cohort of patients allergic to tree pollen with serological positivity to Bet v1 [39]. However, we demonstrate a relevant cohort of individuals with SPT positivity to alder and/or hazel, but not birch pollen. Although complete cross-reactivity of *Betulaceae* major allergens in IgE-binding was observed [40], the response patterns to birch, hazel and alder allergen immunotherapy (AIT) can differ depending on individual sensitization profiles [41, 42]. Our rates of cross-sensitization between birch, alder, and hazel in SPTs ranged from 73.6 to 84.7 %. However, our study cohort contained up to 7.8 % non-birch-sensitized patients with positive SPTs to other trees. In an Italian region without any birch trees, patients suffering from respiratory allergies showed isolated sensitization to hazel pollen at a surprisingly high rate of 13.5 % [43]. Although sensitization to alder and hazel in SPTs may be due to primary sensitization to non-*Betulaceae* allergen sources such as grass pollen, IgE sensitization to hazel-specific allergenic compounds should be suspected in at least some cases. Clinical trials have proved the efficiency of AIT with birch extract in the total-tree pollen season for birch-sensitized patients only [42]. The therapeutic coverage of non-birch-, but alder- and/or hazel-sensitized patients is to be expected. However, AITs containing mixtures of birch, alder, and hazel extracts in the treatment of those patients is questionable, since the efficacy depends on the dose of clinically relevant allergens, and a high cumulative dose is recommended in AIT guidelines [44]. To the best of our knowledge, no clinical trial has yet proven the efficacy of, for example, an isolated birch AIT in tree pollen allergic patients without birch sensitization. This finding may also be relevant in HDM allergy among others.

Overall, our study has some limitations due to the retrospective setting and referral situation for patients with suspected aeroallergies. However, a large dataset of SPTs was collected, including the major, clinically relevant aeroallergens

in Germany for symptomatic patients over 20 years, showing current trends with regard to changes in sensitization rates and pattern. In exceptional cases, patients with unusual mono-sensitization profiles should be studied in detail for selection of the optimal AIT. Future national, population-based studies are needed to corroborate our findings of increasing sensitization rates in Germany.

Contributions

CB and TB designed the study, BW provided pollen data, CB, SF, TF, TB collected patient data, JG and SG extracted and analyzed the data, all authors discussed the data, CB and TB drafted the manuscript, and all authors reviewed and amended the manuscript.

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