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# Allergic Rhinitis to Weed Pollen in Germany: Dominance by Plantain, Rising Prevalence, and Polysensitization Rates over 20 Years

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**Keywords**
Aeroallergen · Weed pollen · Mugwort (*Artemisia vulgaris*) · Ragweed (*Ambrosia artemisiifolia*) · Ribwort plantain (*Plantago lanceolata*) · Chamomile (*Matricaria chamomilla*) · Nettle (*Urtica dioica*) · Oilseed rape (*Brassica napus*) · Allergic rhinitis · Skin prick test

**Abstract**
***Background:*** In contrast to the 3 major aeroallergens tree pollen, grass pollen, and house dust mites, allergic rhinitis caused by herbal pollen has received comparatively little attention in recent clinical studies. Since various weeds flower during summer until fall, allergic rhinitis to weeds may be underdiagnosed and/or mistakenly diagnosed as grass pollen allergy. ***Objective:*** To investigate (i) the currently most frequent weed allergy between mugwort, ragweed, plantain, chamomile, nettle, and oilseed rape and (ii) time trends in prevalence of sensitization to weed pollen in the middle of Germany over the last 20 years. ***Methods:*** This study, the largest of its kind to date, monocentrically evaluated the prick test results of a total of 6,220 patients with suspected RCA over a period of 20 years (1998–2017). ***Results:*** In the study cohort, sensitization rates to plantain almost doubled from 26.6% in the decade 1998–2007 to 50.5% in 2008–2017. Identical increases were observed for ragweed, while sensitization rates for mugwort stayed largely unchanged. The most prominent increase in positive skin prick tests to plantain and ragweed pollen was mainly observed in younger patients. Further, we identified a trend toward polysensitization, currently dominated by plantain and ragweed. Sensitization to weed pollen was found to be highly associated with additional sensitizations to grass and/or birch pollen. ***Conclusion:*** Plantain is currently the best choice to screen rhinitis patients for weed allergy which identifies 86% of all weed-sensitized individuals, at least in Germany. Over the last 20 years, we demonstrate a significant rise in the total number of weed pollen sensitization as well as increases in polysensitization, predominantly in younger patients.

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## Introduction

The prevalence of allergic sensitization especially to airborne allergens increased significantly over the last decades, resulting in a high socioeconomic burden [1–4].

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Symptomatic allergic rhinitis and bronchial asthma during summertime and autumn may be caused by various weed pollen allergens. In a recent study on effects of climate change on pollen allergy in Europe, sensitization rates to ragweed (member of the weed plants) were projected to more than double in Europe, from 33 to 77 million people, by 2041–2060 [5]. Caused by a larger geographical dissemination of ragweed, the greatest proportional increases are expected in countries where sensitization rates are currently low (e.g., Germany, Poland, France). In addition, higher pollen concentrations and a longer pollen seasons may also increase the severity of symptoms [5]. Patients with suspected grass pollen allergy should be evaluated for additional allergies to weed pollen, due to overlapping flowering periods and considerable rates of cosensitization [6]. Of note, the commonly used umbrella term "weed pollen" is only an inadequate auxiliary construct because it refers to several botanically quite different plant groups. Nonlignifying and nonpersevering plants are grouped together as weeds. They include culinary herbs, medicinal plants, food plants and plants that cannot be used by humans or domestic animals [7]. Ragweed, mugwort, and chamomile are botanically closely related and belong to the family of *Asteraceae (Compositae)*. These are herbaceous plants whose inflorescences usually consist of densely standing individual blooms [8]. The different types of plantain belong to the family of *Plantaginaceae* with quite diverse phenotypes, which makes identification by nonspecialists somewhat difficult. Nettle plants are representatives of the family of *Urticaceae*, often easily detectable by their urticating hairs. Oilseed rape belongs to the family *Brassicaceae*, cruciferous plants.

The prevalence of sensitization to one or more aeroallergens in Germany according to the "German Health Interview and Examination Survey for Adults" (DEGS1) from 2008 to 2011 was calculated to be 33.6% of the general population based upon specific IgE analyses [9]. Of note, 11.2% of the general population displayed a sensitization to weed pollen (summarizing different kinds of ragweed and mugwort) [9]. Sensitization to grass pollen, birch pollen, and house dust mites are most common and clinically relevant, with those against ragweed and mugwort occurring concomitantly [10–12]. Distinguishing cosensitization from cross reactivity, however, is difficult in clinical practice [13]. The most extensive data set stems from the multinational Ga$^2$len network as multicenter, open-label, skin prick test (SPT) study in 14 European countries. By using this standardized SPT panel, analyses of weed pollen comprised exclusively mugwort, ragweed, and pellitory [14, 15]. The highest sensitization rates to weed pollen were detected in Hungary (ragweed 53.8%, mugwort 44.3%) [16]. Pellitory sensitization was mostly observed in Italy (33.2%), with low frequency in Germany (6.9%). The major populations of ragweed are found in South-East Europe (ranging geographically from southern France, northern Italy, and Croatia to Serbia). Hungary is considered one of the most ragweed-infested areas in Europe. In addition to the naturally occurring seed dispersal of ragweed pollen, the anthropogenic impact by transport and trade exchange appears to accelerate the ragweed distribution [17]. Due to the increasing concentrations of ragweed pollen by expanding populations in Germany and elsewhere, recent studies mainly focus on sensitization to ragweed pollen [18]. The "National Health and Nutrition Examination Survey" calculated that about 26% of the entire population of the United States is sensitized to ragweed, as determined by SPT [19]. Ragwitek®, a sublingual immunotherapy for ragweed allergy, was approved in the United States by the FDA in 2014 [20].

The most clinically relevant weed pollen causing allergic symptoms in Germany seem to be mugwort and ragweed [16]. No other weed pollen was investigated in greater detail, and we are not aware of any studies focusing on sensitization profiles to multiple different weed pollen. Therefore, the primary aim of this study was to investigate the prevalence of allergic sensitization to various weed pollen in the central region of Germany over a period of 20 years. Secondary, we analyzed cosensitization of the weed pollen mugwort, plantain, ragweed, nettle, chamomile, and oilseed rape. Finally, cosensitization of the most prominent weed pollen mugwort, plantain, and ragweed with the most important outdoor aeroallergens birch and grass pollen was addressed.

## Materials and Methods

*Study Population*

We retrospectively compiled data of 6,220 patients who underwent SPT with aeroallergens in our tertiary referral center at the Department of Dermatology, Venereology and Allergology at the University Medical Centre Göttingen located at the geographical center of Germany. The study period comprised the years 1998–2017. Subgroup analysis was performed for the decades 1998–2007 ($n$ = 3,539) and 2008–2017 ($n$ = 2,681). Further subgroup analyses were performed on patients who received the extensive weed SPT panel consisting of all 6 investigated weed pollen (1998–2007, $n$ = 652; 2008–2017, $n$ = 385). SPT with weed pollen was performed as part of an extensive standard diagnostic panel, and not in an aimed manner. Hence, we can largely exclude a selection bias due to more or less strict indication for SPT with weed pollen over the years. The some-

| Allergen | Prevalence (positive SPT/ total patients) 1998–2007 | Prevalence (positive SPT/ total patients) 2008–2017 | Change | Significance level $\chi^2$ test |
|---|---|---|---|---|
| Plantain | 26.6% (396/1,489) | 50.5% (562/1,113) | +89.9% | <0.0001 |
| Ragweed | 21.4% (248/1,159) | 36.3% (425/1,170) | +69.6% | 0.0015 |
| Chamomile | 35.9% (388/1,081) | 43.4% (310/715) | +20.9% | <0.0001 |
| Oilseed rape | 20.4% (362/1,771) | 31.3% (431/1,378) | +53.4% | <0.0001 |
| Mugwort | 26.1% (405/1,551) | 27.4% (326/1,188) | +5.0% | <0.0001 |
| Nettle | 14.2% (168/1,187) | 25.0% (192/769) | +76.1% | 0.44 |

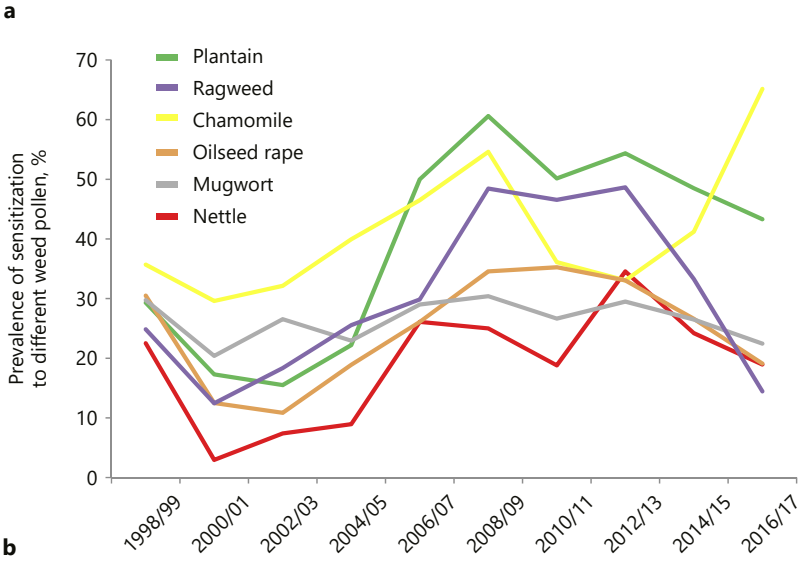


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**Fig. 1.** Prevalence of sensitization rates to the 6 weed pollen investigated (plantain, ragweed, chamomile, oilseed rape, mugwort, nettle), diagnosed by positive SPTs over 20 years. **a** Results are shown split into 2 decades, 1998–2007 ($n$ = 3,539 patients) and 2008–2017 ($n$ = 2,681 patients), with total numbers of positive SPTs and total number of all tested patients to the respective allergen being shown. The increase in prevalence from 1998 to 2007 to 2008 to 2017 is depicted in the category "change." **b** More detailed time trends are depicted for all patients included ($n$ = 6,620 patients), depicted in 2-year intervals. The detailed data sets can be found in online supplementary Table S1, including total numbers of the tested allergen, total number of patients with positive SPT, with percentage specification, as well as the confidence interval. SPT, skin prick test.

what lower number of patients in the second decade investigated is caused by general structural changes in the allergy unit (reduced personnel), but not by more selective testing. Briefly, test results of all patients are recorded in local databases and, after anonymization, transmitted to the IVDK central office at the University of Göttingen. This retrospective study has been reviewed and approved by the local Ethics Committee at the University Medical Center Göttingen.

## Methods

SPT was performed according to national guidelines [21], with sensitization being defined as a positive SPT. Commercially available allergen extracts were used for all patients. Over the 20 years covered in this study, pollen extracts were purchased from 6 different companies: Allergopharma (Reinbek, Germany), ALK-Abellò (Reinbek, Germany), Stallergenes (Antony, France), Bencard (Munich, Germany), HAL (Leiden, Netherlands), and Novartis (Basel, Switzerland). SPT was performed on the back or the forearm with standardized solutions of allergens. Histamine hydrochloride (10 mg/mL) was used as positive control and saline solution as negative control (both from Allergopharma). Different from current standards, a reaction with an average wheal diameter ≥2 mm was assessed as positive; this parameter was consistent over the 20 years covered in this study. At the time of implementation of SPTs in the late 1990s, wheal reactions ≥2 mm were regarded as positive [22, 23]. Especially in epidemiological studies, the classification of wheals with a diameter of <3 mm as a positive reaction was explicitly recommended at this time [24]. At present, only diameters ≥3 mm should be evaluated as positive results [21]. This historical reading parameter may lead to overestimation of positive SPTs in our study. Remarkably, the same 3 persons always evaluated the test reactions during the entire 20-year observation period, so that subjective interindividual differences due to changes in the evaluators were excluded.

*Statistical Analysis*

Data was analyzed using the statistical analysis software SAS©, version 9.4 (SAS Institute, Cary, NC, USA). Differences in proportions between disjunct subgroups of patients were tested for significance using the chi-square test. Each figure or table contains information on the significance levels in the legend: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ were considered significant.

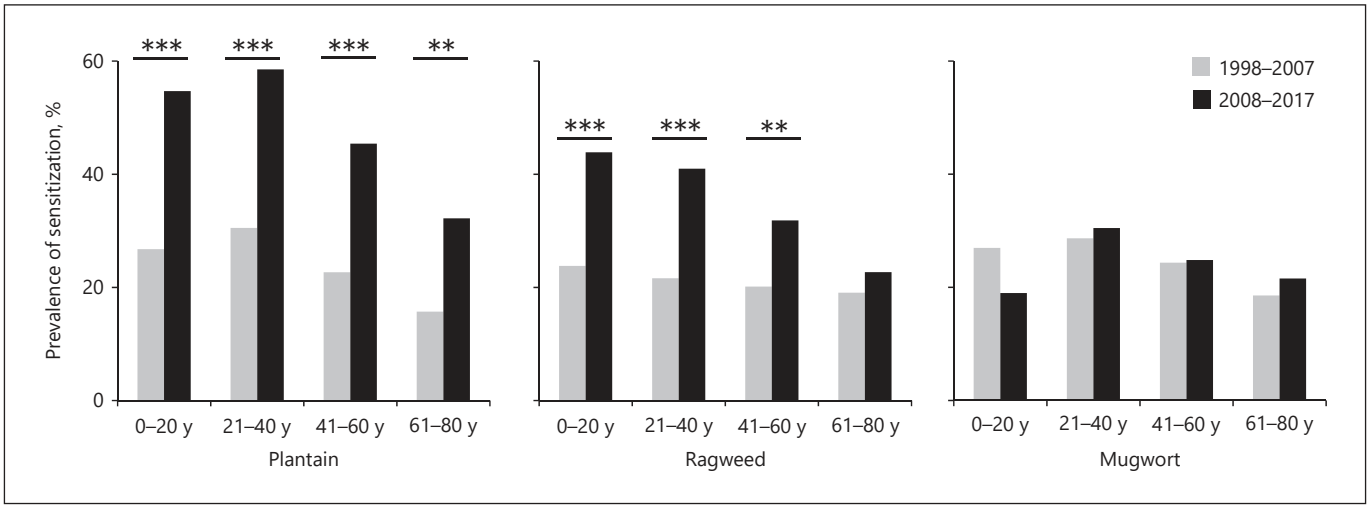


**Fig. 2.** Prevalence of positive SPT to plantain, ragweed, and mugwort regarding age distribution (0–20, 21–40, 41–60, and 61–80 years) during the 2 decades, 1998–2007 (plantain [$n$ = 1, 486 patients]; ragweed [$n$ = 1, 158]; mugwort [$n$ = 1, 541]) vs. 2008–2017 (plantain [$n$ = 1, 110 patients]; ragweed [$n$ = 1, 158]; mugwort [$n$ = 1, 188]). Significance levels are depicted comparing the corresponding age groups between the first and second decade for each allergen by chi-square test. Significance levels: ** $p < 0.01$, *** $p < 0.001$.

## Results

The SPT results of 6,220 patients with suspected allergic rhinitis or bronchial asthma for weed pollen sensitization were investigated. For some analyses, the 2 decades 1998–2007 (3,539 patients) and 2008–2017 (2,681 patients) were compared in greater detail to identify trends. Age and sex distribution were largely constant over time, with more women being tested (63.3 vs. 36.8%; online suppl. Fig. S1; see www.karger.com/doi/10.1159/000504297 for all online suppl. material). Total patient count was about 25% lower in the second decade with 2,681 patients as compared to 3,539 patients in the first decade. However, ragweed pollen was tested in about the same number of patients in both decades, but the number of patients tested with chamomile and nettle pollen was reduced to 2 thirds in the second decade. Contrasting the results of the 2 decades, we found a highly significant increase in sensitization rates to all tested weed pollen over time, except for nettle (Fig. 1a). Most prominently, sensitization rates to plantain almost doubled (+89.9%), and ragweed increased by 69.6% during these 2 decades (Fig. 1a). In contrast, the sensitization rate to mugwort remained mostly unchanged (26.1 vs. 27.4%). In-depth analysis of 2-year-intervals of our study period revealed an initial decline in sensitization frequencies to all weed pollen tested from 1998/1999 to 2001/2001, followed by an increase until 2006/2007 (Fig. 1b; extended data in online suppl. Table S1). Afterward, the sensitization to most weed pollen was almost constant, followed by a moderate decline from 2012/2013 on. Exceptions were frequencies of sensitization to ragweed pollen with a dramatic decrease from 49% in 2012/2013 to 16% in 2016/2017 and chamomile pollen with an increase from 34% in 2012/2013 to 68% in 2016/2017.

Interestingly, compared to the first decade the most pronounced increase in sensitization to plantain and ragweed, respectively, occurred among younger people (0–40 years) from 2008–2017 (Fig. 2). The sensitization rate to plantain and ragweed pollen almost doubled in younger people with highly significant changes, and similar trends were observed in patients >40 years of age. However, sensitization rates to mugwort remained unaltered during these 2 decades. Since clinically relevant weed allergy may be underdiagnosed due to overlapping flowering times with the more prominent birch or grass pollen, we investigated cosensitization of these 3 most relevant weed pollen with birch and grass pollen sensitization. Positive SPTs to birch and grass pollen were associated with sensitizations to the most important weed pollen plantain or ragweed in >75% of patients at all times, without significant changes during the study period (Fig. 3). This finding underlines the necessity to carefully assess the clinical significance of positive SPT results, optimally by both nasal challenge and serological analyses. Since

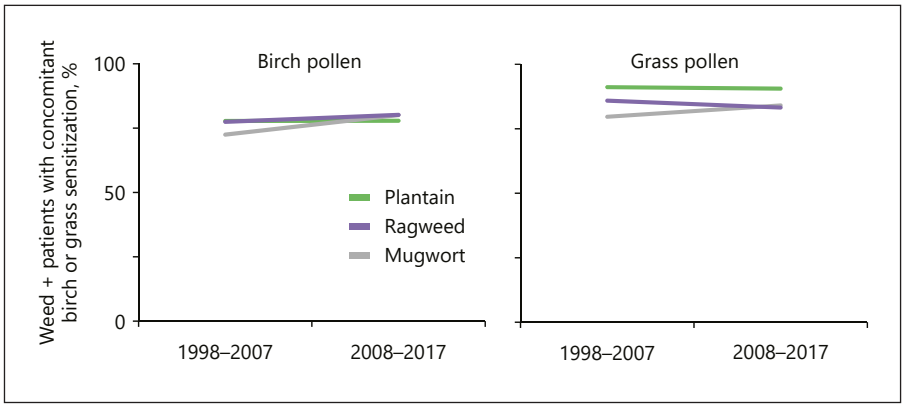


**Fig. 3.** Percentage of patients with positive SPTs to weed pollen (plantain, ragweed, or mugwort) with additional sensitization to grass or birch pollen in the years 1998–2007 ($n$ = 652 patients) and 2008–2017 ($n$ = 385 patients). Data were collected from subgroup analyses of patients who underwent SPTs with all 6 weed pollen extracts (plantain, ragweed, chamomile, oilseed rape, mugwort, and nettle).

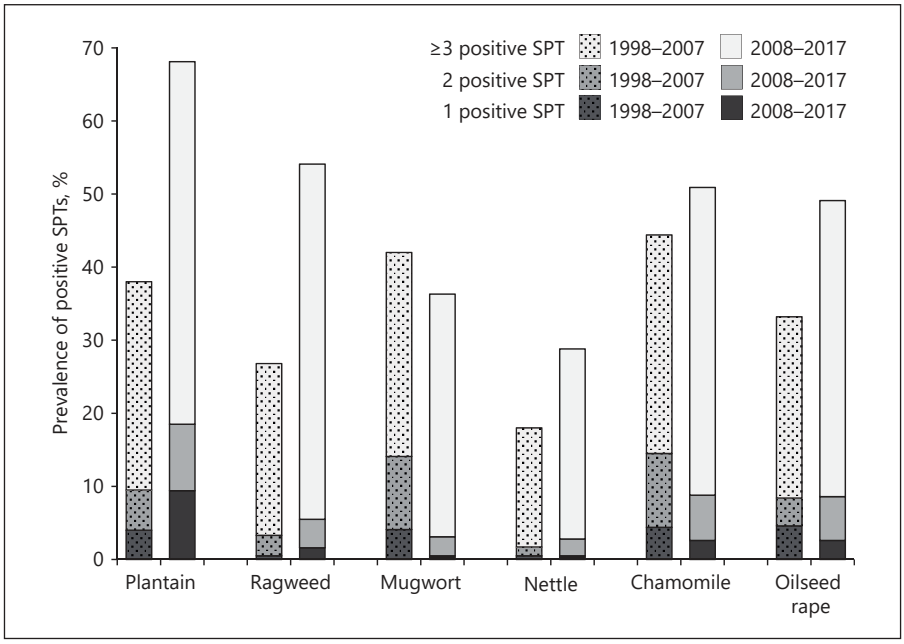


**Fig. 4.** Prevalence of positive SPTs to weed pollen (plantain, ragweed, chamomile, rape, mugwort, nettle) in the subpopulations of patients who underwent SPTs with all 6 weed pollen extracts in the years 1998–2007 ($n$ = 652) and 2008–2017 ($n$ = 385). In each column, the proportion of patients with positive SPT to 1, 2 or ≥3 of these 6 pollen allergens is marked. SPT, skin prick test.

this is a retrospective study, no blood samples were available to differentiate truly cosensitized from cross-sensitized patients by serological analysis.

With the aim to dissect sensitizations to rather uncommon weed pollen such as chamomile, nettle, and oilseed rape, we performed subgroup analyses on patients who were tested by the extensive weed SPT panel consisting of all 6 weed pollen investigated (1998–2007, $n$ = 652 patients; 2008–2017, $n$ = 385 patients). In the first decade of our study, we found no sensitization to any weed pollen in 28.8% of patients, whereas only 12.5% of patients were identified with no sensitization from the second decade (online suppl. Table S2). More interestingly, monosensitization to one of the 6 weed pollen tested (plantain, ragweed, mugwort, nettle, oilseed rape, chamomile) was rare, independent of the decade (18.1 vs. 17.1%). On the opposite end of the spectrum, a positive SPT to all 6 pollen was found in 5.4 vs. 7.8% of individuals. In the second decade (2008–2017), plantain sensitization was dominant either individually (9.4%) or in combination with positive SPTs to other weed pollen. Figure 4 depicts positive SPTs to other weed pollen investigated, from the perspective of the individual weed. Positive SPTs to ≥3 weed pollen including plantain revealed the highest rates (1998–2007: 28.5%; 2008–2017: 49.6%), whereas positive SPTs to nettle were almost exclusively observed in combination with several other weed sensitizations. In addition, sensitization to ragweed increased in recent years (Fig. 4). While 1.6% (6/385) of patients displayed a monosensitization to ragweed only, the proportion of ragweed-sensitized patients

to at least 3 different weeds doubled over time (1998–2007: 23.5%; 2008–2017: 48.6%). Further, the number of patients with at least 3 positive SPTs to the 6 weed pollen increased for all weed pollen investigated from the first decade to the second. However, we did not identify a pattern of related allergens in poly-sensitized patients. Therefore, all profiles of positive SPTs to the 6 allergens with >3 patients per group were depicted in a modified Venn diagram to identify overlapping pollen sensitizations (Fig. 5). Plantain and ragweed sensitizations were found to mostly coincide in our patient cohort from the last decade with 86.1% positive SPTs to plantain and 64.2% positive SPTs to ragweed, respectively. However, this analysis did not reveal a pattern that allowed grouping positive SPTs according to the botanical relationship of the plants.

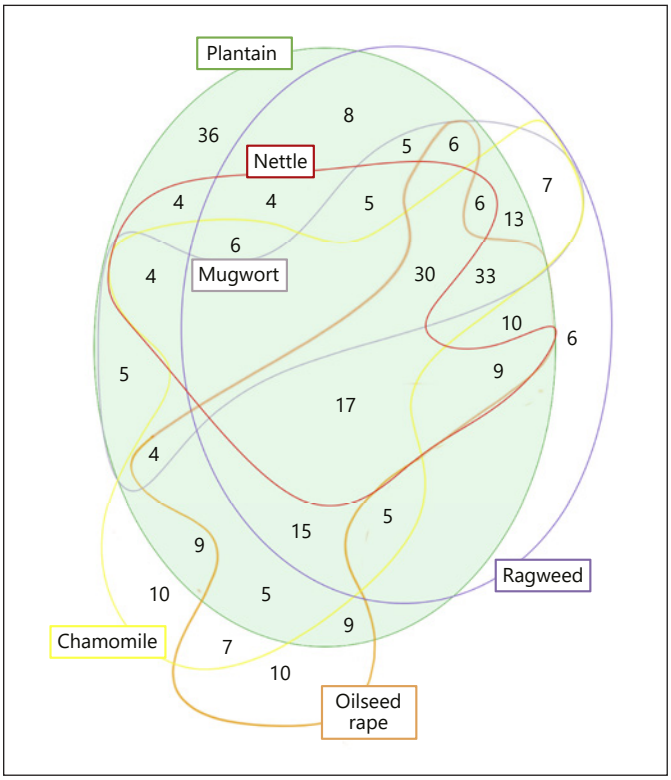


**Fig. 5.** Venn diagram displaying the overlapping profiles of weed pollen sensitizations in the last decade, 2008–2017 ($n$ = 385 patients). Only profiles with >3 patients (>1%) are depicted. Data were collected from subgroup analyses of patients, who underwent SPTs with all 6 weed pollen extracts.

## Discussion

To our knowledge, this is the first investigation on the prevalence of allergic sensitizations to weed pollen including time trends over 20 years. Overall, as detected by SPT the prevalence of allergic sensitization to weed pollen increased significantly. High increases were detected in the sensitization rates to plantain, ragweed, nettle, chamomile, and oilseed rape pollen. Our results differ from the German DEGS1-study from 2008 to 2011 ($n$ = 7,025 individuals) due to different selection of individuals and different methodology for determination of allergic sensitization [9]. The DEGS1-study found an average sensitization rate of 11.2% to ragweed and mugwort, respectively, by analysis of specific IgE. Comparable results were obtained in the German KiGGS-study in children and adolescents from 2003 to 2006 ($n$ = 12,988 individuals) [25]. Unfortunately, the single investigated weed pollen in this survey was mugwort with a prevalence of 10.9% according to analysis of specific IgE. However, higher rates were expected in our study cohort since we did not perform a population-based study such as the DEGS1- and KiGGS studies, but we diagnosed patients being referred for suspected allergic rhinitis or bronchial asthma. Further, we performed SPTs, while the DEGS1- and KiGGS-study analyzed specific IgE to exclusively mugwort, and additionally ragweed in DEGS1. Most experts agree that SPT has the best predictive value for allergy-related disease [26], especially since SPTs display a higher specificity than analysis of specific IgE levels [27]. The most frequent allergen plantain, as determined in our study cohort by comprehensive analysis, was never investigated in these population-based studies. Further, the results from the European prick test study (Ga$^2$len network) reported a prevalence of sensitization in Germany to ragweed of 14.4%, to mugwort of 22.5%, and to pellitory of 6.9% [16].

Earlier data showed a peak prevalence in allergic sensitization in late puberty and early adulthood [28]. In a longitudinal study with randomly selected Danish pupils who underwent multiple SPTs over 20 years, a significant increase in the overall sensitization rate to aeroallergens was observed between the age cohort 7–17 years and renewed SPTs 20 years later at the age of 27–37 years [2]. In another longitudinal study on Swedish pupils, aeroallergen SPTs from 1996 compared with SPTs 10 years later in the same patients found a significant increase by 30% of positive aeroallergen SPTs [3]. The only investigated weed pollen in this study was mugwort, and sensitization rates to mugwort climbed by 2.6-fold. According to this data, we found an almost doubled sensitization rate of ragweed in the age groups of 0–20 and 21–40 years. Since ragweed is a neophyte in Germany, increasing ragweed populations have been registered since the 2000s predominantly

in the South and the East of Germany [18, 29]. Rueff and colleagues published a prevalence of 19.5% ragweed-sensitized patients in Southern Bavaria ($n$ = 190, SPT) [18]. Significant variation of sensitization rates to ragweed has been reported in European countries, the extremes ranging from 2.3% in Finland to 53.8% in Hungary [16].

The results of our study clearly delineate noteworthy changes in the sensitization profiles to plantain in recent years, with a doubled-sensitization prevalence of 50.5% in patients with symptomatic allergic rhinitis. While ragweed sensitization follows a similar trend, sensitization rates to mugwort were found to remain largely unchanged over time. Detailed analyses of the SPTs demonstrated that the increased sensitization rate to almost all weed pollen, except for mugwort, is primarily based on an increased polysensitization to different weed pollen. Especially the prevalence of positive SPTs to ≥3 weed pollen grew larger. Several investigations already observed a drift to increased multisensitization to aeroallergens [30, 31]. Particularly, an early onset of allergic sensitization is associated with multisensitization to aeroallergens [2, 3, 32]. Other data describe a rise in sensitization to grass and birch pollen [2, 3], the dominating outdoor allergens in Germany [9]. Interestingly, cosensitization to birch and grass pollen in our cohorts was consistent on a high level over 20 years. These results are in line with other studies, such as a study from Northern France displaying similar high prevalence rates as detected by SPTs [6]. They found cosensitization to grass pollen in 94.3 and 71.4% to birch, respectively, almost identical to our results. In-depth analysis with recombinant allergens revealed that 94.3% of the patients with positive SPT to plantain and grass displayed specific IgE to Phl p1/5, 65.7% to Bet v1, 17.6% to Art v1, and 34.3% to Pla l1. Inhibition experiments displayed only 37.1% of the patients having a "true" plantain sensitization [6]. Other data showed a high association with grass pollen and cross reactivity to determinants such as Phl p5, without clinical relevance [10, 33]. On the other hand, an association of 86% to Pla l1 was demonstrated in patients with plantain allergy, which was supported by patient history, SPTs, and serological analyses [34]. Thus, available data are inconsistent, and the investigations were done in rather small groups of patients and different geographic areas. In conclusion of our large study cohort, plantain is probably an underestimated, but relevant aeroallergen. The current German Guideline recommends SPTs of 4 different weed pollen in adults: pellitory, mugwort, ragweed, and plantain [21]. The recommended test panel for children includes no other weed pollen than mugwort and ragweed. Additionally, the "minimum test battery" of the European Galen study recommended testing of mugwort only [15]. From our results, we recommend SPT with the 3 clinically most relevant weed pollen: mugwort, ragweed, and plantain, with plantain being the most reliable allergen to screen for weed allergy. Indeed, we suspect that plantain is a potentially underestimated allergen due to lack of comprehensive investigations.

The lack of clinical details of the patients limits our analyses to the detection of sensitization rates. Further, the selection of patients at a university hospital does not necessarily reflect the sensitization profiles in the general population although the major issues should be reflected. Six different companies produced the SPT extracts in this study over 20 years. In contrast, only 3 experienced experts performed all SPTs in this study, thus diminishing individual differences in performing and reading SPTs. In summary, sensitization against weed pollen is an increasing problem. The remarkable increase in sensitization rates may predict a continuous increase in clinical manifestation of allergic airway disease.

## Statement of Ethics

This retrospective study has been reviewed and approved by the local Ethics Committee at the University Medical Center Göttingen.

## Disclosure Statement

None of the authors have a conflict of interest in relation to this work. The authors have no ethical conflicts to disclose.


## Funding Sources

None.


## Author Contributions

S.F., J.G., and T.B.: designed the study. T.F.: collected data. J.G.: extracted and compiled data; all authors discussed data. S.F. and T.B.: drafted the manuscript. All authors jointly discussed, reviewed, and amended the manuscript. All authors reviewed the final manuscript version and consented to its submission.

## Availability of Data and Materials

Data and materials of this study are available at the authors on request.

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