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Pollen season is reflected on symptom load for grass and birch pollen-induced allergic rhinitis in different geographic areas—An EAACI Task Force Report

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Abstract

Background: The effectiveness of allergen immunotherapy (AIT) in seasonal allergic rhinitis (AR) depends on the definition of pollen exposure intensity or time period. We recently evaluated pollen and symptom data from Germany to examine the new definitions of the European Academy of Allergy and Clinical Immunology (EAACI) on pollen season and peak pollen period start and end. Now, we aim to confirm the feasibility of these definitions to properly mirror symptom loads for grass and birch pollen-induced allergic rhinitis in other European geographical areas such as Austria, Finland and France, and therefore their suitability for AIT and clinical practice support.

Methods: Data from twenty-three pollen monitoring stations from three countries in Europe and for 3 years (2014-2016) were used to investigate the correlation between birch and grass pollen concentrations during the birch and grass pollen season defined via the EAACI criteria, and total nasal symptom and medication scores as reported with the aid of the patient's hay-fever diary (PHD). In addition, we conducted a statistical analysis, together with a graphical investigation, to reveal correlations and dependencies between the studied parameters.

Results: The analysis demonstrated that the definitions of pollen season as well as peak pollen period start and end as proposed by the EAACI are correlated to pollen-induced symptom loads reported by PHD users during birch and grass pollen season. A statistically significant correlation (slightly higher for birch) has been found

Abbreviations: AIT, allergen immunotherapy; AR, Allergic Rhinitis; GA^{2}LEN, Global Allergy and Asthma European Network; EAACI, European Academy of Allergy and Clinical Immunology; PHD, patient's hay-fever diary; PS, Pollen Season; PPP, Peak Pollen Period; RNSA, French Aerobiology Network; TNSMS, Total Nasal Symptom and Medication Score; WNMS, Weighted Nasal Medication use Score.

Oliver Pfaar and Kostas Karatzas denote equal contribution.

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between the Total Nasal Symptom and Medication Score (TNSMS) and the pollen concentration levels. Moreover, the maximum symptom levels occurred mostly within the peak pollen periods (PPP) following the EAACI criteria.

Conclusions: Based on our analyses, we confirm the validity of the EAACI definitions on pollen season for both birch and grass and for a variety of geographical locations for the four European countries (including Germany from a previous publication) analyzed so far. On this basis, the use of the EAACI definitions is supported in future clinical trials on AIT as well as in daily routine for optimal patient care. Further evaluation of the EAACI criteria in other European regions is recommended.

KEYWORDS
allergen immunotherapy, allergic rhinitis, geographic differences, peak pollen period, pollen concentration, pollen season

1 | BACKGROUND

Allergic rhinitis (AR) is a significant health problem due to the symptom load as well as its impact to the quality of life of the affected part of the population. It also implies a high economic burden.[1-3] The cause of the disease is an immunological abnormality leading to IgE-mediated hypersensitivity reactions resulting from the exposure to allergens.[3] The treatment of choice for dealing with the causes of AR rather than its symptoms is allergen immunotherapy (AIT) that aims to promote tolerance of the immune system toward allergens.[4-7] AIT has been shown to be highly efficacious in the treatment of allergic diseases such as allergic rhinoconjunctivitis with or without allergic asthma,[8] including improvement of symptoms, quality of life, long-term symptom control and preventive potential.[9-11] However, clinical effects in clinical trials demonstrated that pollen exposure has a direct influence on the level of AIT efficacy measured.[12]

Overall, the definition of pollen season (PS) and peak pollen periods (PPP) should follow a harmonized application of pollen exposure criteria, taking into account biogeographical differences that may reflect local climate and phenology.[13,14] Such a definition has been proposed in a recently published Position Paper of the European Academy of Allergy and Clinical Immunology (EAACI),[15] summarized for birch *(Betula)* and grass (Poaceae) in Table 1. In the framework of this initiative, we have recently verified the robustness of these definitions for grass pollen in Germany, making use of 5-year measurements from up to 40 monitoring stations in the country.[16] Moreover, the correlation between birch and grass pollen concentrations and actual symptom loads, as reported by users of patient's hay-fever diary (PHD),[17] during the defined birch and grass pollen seasons, has been demonstrated for the Berlin–Brandenburg region in Germany for three consecutive years: 2014, 2015, and 2016.[18]

Following the previous study in Germany,[18] in this article we present the relationship between birch (*Betula*) and grass (Poaceae) pollen concentrations and actual symptom load and concomitant medication use, for three additional European regions in Austria, Finland, and France, for the same 3-year period (2014-2016) as in the previous research.[18] As already emphasized by the expert panel, comprising of aerobiologists and clinicians in the respective EAACI Position Paper,[15] the given definitions should be regarded as tentative and for critical evaluation.

TABLE 1 Definitions of pollen seasons for Birch and Grass according to the EAACI position paper (modified from[15]; nota bene: The "high pollen days" criterion is not shown as it has not been analyzed in the current study)

	Pollen season	High pollen season (or "Peak pollen period")
Birch	Start: 1st day of 5 d (out of 7 consecutive days), each of these 5 d with ≥10 pollen/m^3 and with a sum of these 5 d of ≥100 pollen/m^3 End: Last day of series of 5 d (out of 7 consecutive days) with ≥10 pollen/m^3 and with a sum of these 5 d of ≥100 pollen/m^3	Start: 1st day of 3 consecutive days, each with at least ≥100 pollen/m^3 End: Last day of at least 3 consecutive days, each with ≥100 pollen/m^3
Grass	Start: 1st day of 5 d (out of 7 consecutive days) each of these 5 d with ≥3 pollen/m^3 and with a sum of these 5 d of ≥30 pollen/m^3 End: Last day of series of 5 d (out of 7 consecutive days) with ≥3 pollen/m^3 and with a sum of these 5 d of ≥30 pollen/m^3	Start: 1st day of 3 consecutive days, each with at least ≥50 pollen/m^3 End: Last day of at least 3 consecutive days, each with ≥50 pollen/m^3

This report aims to analyze whether birch and grass pollen season and peak pollen periods, as defined by the EAACI, can be identified in different regions in Europe and, more importantly, whether these definitions reflect the development of seasonal symptoms.

2 | MATERIALS AND METHODS

The selection of these European regions considered the availability of sufficient pollen data as well as symptom data via the PHD. The pollen types that were included in the analysis were birch (*Betula*) and grass (Poaceae) in the years of 2014, 2015, and 2016. We therefore considered one region per country: the Pannonian lowlands region of Austria, the southern region of Finland, and the Rhone-Alps region of France. We used data from a total of twenty-three pollen monitoring stations (Figure 1 and Table S1).

Data of daily AR related to symptom levels and concomitant medication use are reported on a voluntary, regional, and anonymized basis through a web-based Pollen App, which includes the PHD (https://pollendiary.com). The number of symptom reports was highly variable: The mean yearly number of PHD users (ie, a 12-month period statistic, rounded to the closest integer) reporting symptoms for the Austrian, Finnish, and the French region was 138, 37, and 17 for year 2014; 118, 21, and 18 for year 2015; and 106, 14, and 16 for year 2016.

For this study, we have considered the daily average pollen concentration (in pollen grains/m^3) from all monitoring stations for birch and grass. Hereafter, the PHD data were processed in order to calculate the Total Nasal Symptom and Medication Score (TNSMS). The details of score calculation have been reported before,[18] and the calculation is also based on prior studies.[19,20] Reported symptoms are influenced by concomitant medication.[21,22] However, different medication classes have different effects in improving allergic symptoms of patients. For this reason, we adopted a Weighted Nasal Medication use Score (WNMS) as reported in detail.[18,20]

All available data were averaged per day in order to represent the mean daily pollen as well as the mean TNSMS levels in all studied regions. To provide a data overview, basic descriptive statistics for the 3 years of study have been presented in Supporting information related to the main daily data (Table S2) and pollen season (Table S3).

A classic approach for data analysis was employed to investigate the correlations between daily symptom and pollen data during the pollen season, following both a parametric (Pearson's r) and a non-parametric (Spearman's ρ) estimation. The correlation coefficients and the associated p-values, indicating statistical significance between the TNSMS and the pollen concentrations (for birch and grass), were calculated for the PS period defined with the EAACI definitions for each pollen type and year. Details can be found in the Supporting information (Appendix S1 : correlation calculations).

We also used a graphical representation of symptom data together with (a) pollen concentrations, (b) PS start and end as well as (c) PPP, to visually represent the temporal variation of symptoms as well as of pollen data for all areas and years of study and to further investigate their relationships (Appendix S1 S2: graphical representation and investigation of data).

3 | RESULTS

The basic descriptive statistics for the three countries are reported in Table S2a-c. In addition, the pollen season and peak pollen period start and end for both pollen types were calculated based on the EAACI definitions ([15], Table S3a,b).

Moreover, the correlation coefficients between the TNSMS and the pollen concentrations (for birch and grass) were calculated for the period characterized from the PS start and end per pollen type and year (Table S4a-b). In addition, we plotted the normalized pollen concentration together with the TNSMS as well as with the total number of PHD reports per day for years 2014, 2015, and 2016 (Figure 2 for a representative result).

A first result is related to the higher mean as well as maximum levels of birch pollen in the Finnish region in comparison to the Austrian and French regions, with a difference of one order of magnitude being witnessed. The situation is reversed when it comes to grass, where the French and then the Austrian regions demonstrate a much higher mean value in comparison to the Finnish region, the

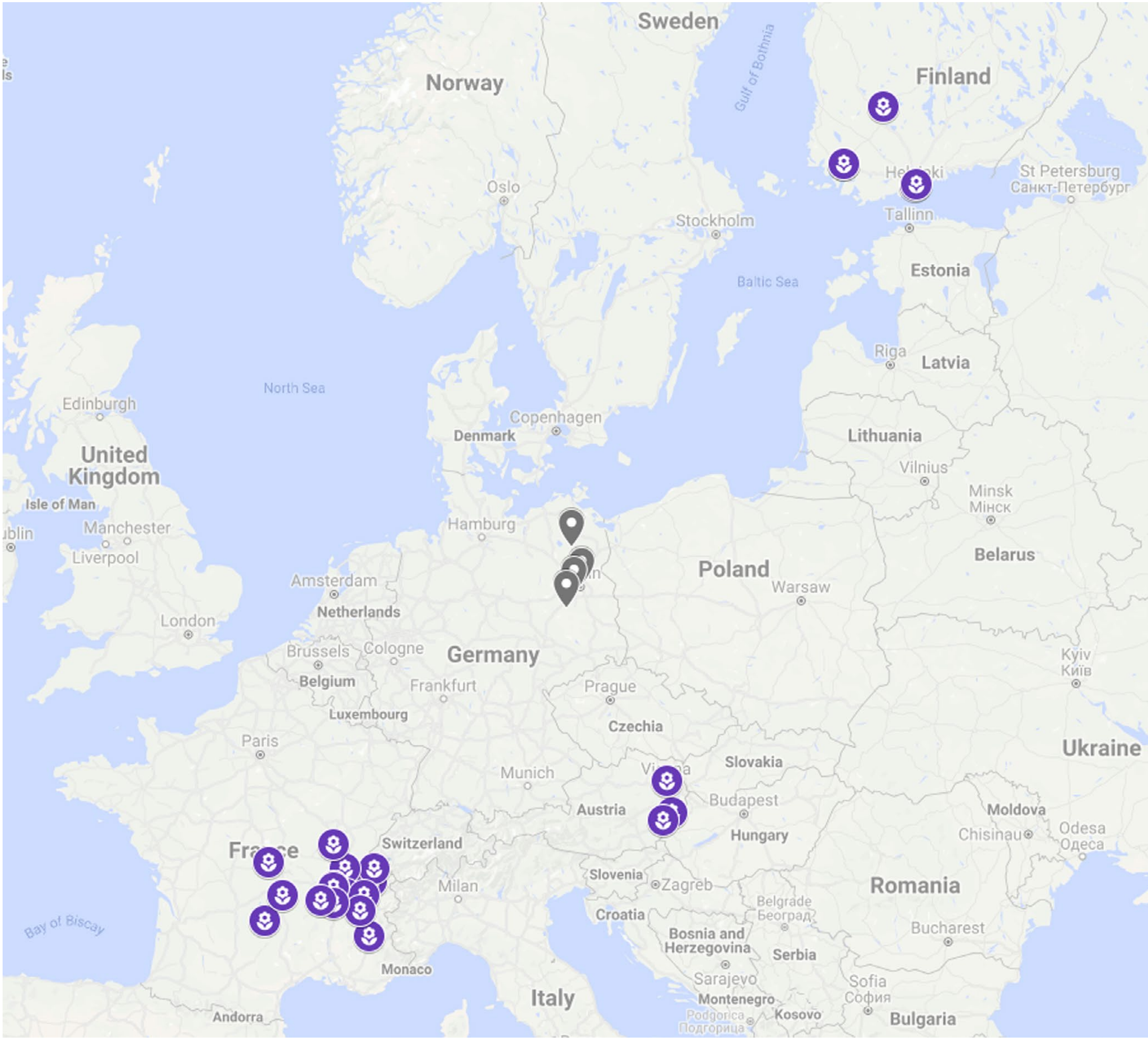


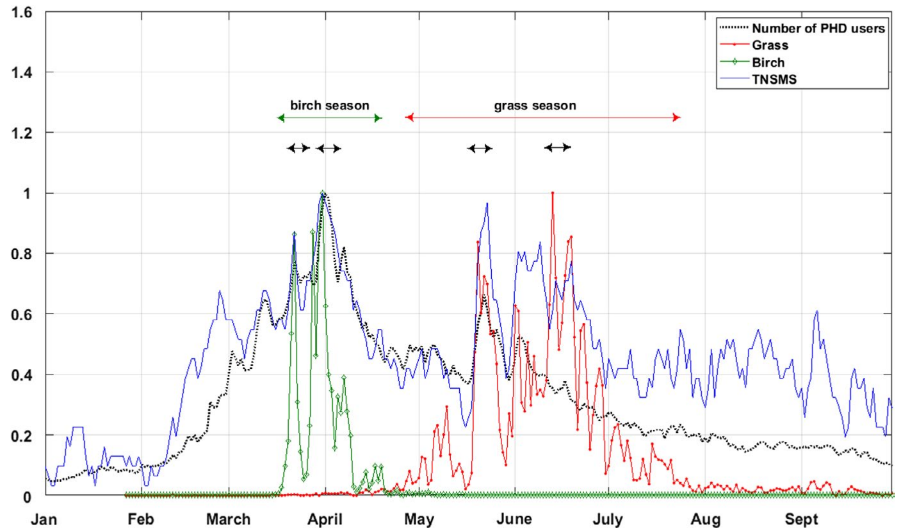
FIGURE 1 Map of the locations of the pollen monitoring station at the southern region of Finland (upper right), the Pannonian lowlands region of Austria (lower right), and the Rhône-Alps region of France (lower left). The stations of the Berlin–Brandenburg area used for Germany in a previous publication ([18]) are also included (middle), for completeness. Map background available via Google Maps ©

latter suggesting a relatively weaker grass pollen season. In terms of TNSMS, the highest mean and maximum levels are reported in the Finnish region, followed by the French and the Austrian regions under study.

The EAACI definitions [15] led to the successful identification of pollen seasons in all areas and for all years, for both pollen types being investigated. More specifically, we found that birch PS started approx. 3-4 weeks later in the southern region of Finland in comparison to the Rhône-Alps region of France and the Pannonian lowlands region of Austria. Grass PS started approx. 6-7 weeks later in the Finnish region in comparison to the French region. In the Austrian region, the grass PS started 1-2 weeks later in comparison to the French region. The ending of the PS for birch arrived earlier in the Austrian and French regions, and is followed by the Finnish region with a delay of approx. 4-6 weeks. PPP appeared in all areas and years, except for 2016 for grass and for the Finnish area. It is worth noting that in some cases like in the French region for grass, we identified several PPP within the PS.

Correlation of pollen concentrations and reported symptoms for the PS-start to PS-end period provide clear evidence concerning the validity of the EAACI definitions. Both correlation coefficients appeared high and were statistically significant in most of the cases (Table S4a-b). The Pearson as well as the Spearman correlation coefficients were higher for birch in comparison to grass in most of the cases, for all areas and years of study, thus suggesting that birch is a better indicator in comparison to grass when it comes to the correlation with the TNSMS for all geographic areas of study. Taking into account the significance level (p-value), the Pearson correlation coefficient in the case of birch ranges from 0.55 (for 2016

FIGURE 2 Temporal variation of the TNSMS, the number of PHD users, and the birch and grass pollen concentrations for 2014 (mean daily values, Pannonian lowlands region of Austria). The PS per pollen type is marked with arrows with a textual label. The multiple PPP starts–ends are denoted with double arrows. The horizontal axis reports month start. The vertical axis reports the normalized (between zero and one) values of the number of PHD users, the grass, and birch pollen daily concentrations and the TNSMS



in the French region) to 0.78 (for 2014 and for the Austrian region) while corresponding values for grass range from 0.48 (for 2015 for the Finnish region) up to 0.79 (for 2014 and for the Austrian region). In the case of Spearman, the highest value for birch reaches 0.84 for the Finnish region (for 2014) and for grass 0.77 for the Austrian region (for 2014). Overall, both coefficients suggest that the pollen season definitions result in high correlations in most cases between pollen concentrations and TNSMS levels.

The analysis showed that for the Austrian region, the maximum TNSMS is reached every year during the birch pollen season between the end of March and the mid of April. Only for 2015, the TNSMS reached its maximum during the last days of May and within the grass pollen season (where the relevant pollen concentration levels reached their maximum mean daily value of 161 pollen grains/m^3, among the 3 years studied).

In the Finnish region, the peaks of TNSMS and birch pollen concentrations coincide in 2014 (abundant birch flowering year) and in 2016 (normal birch flowering year) whereas in 2015, when birch flowered very weakly, a similar correlation was not observed. A clear peak in grass pollen concentrations was detected in 2014 and 2015, and it was reflected in a TNSMS rise in 2015. In 2016, the grass pollen concentrations had multiple, albeit modest peaks.

For the French region, the TNSMS reaches its highest value at the beginning of June (in 2015), or at the end of May (in 2014 and 2016), during the peak period (but not necessarily during the peak days, as defined in[15]) of grass pollen. However, TNSMS levels for the birch season are slightly lower in comparison with the ones recorded for the grass season, with a characteristic peak in the middle of April, during the birch PPP (in 2015 and 2016, with very short peak periods) or some days before (in 2014, when the PPP was noticeably longer). Throughout the birch pollen season, the number of users reporting symptoms per day is closely aligned with both TNSMS levels and pollen concentrations. The picture is quite different for the grass pollen season: The number of symptom reports per day is well matched to the TNSMS levels, but both lines begin to rise at a time when the pollen concentrations are still low.

4 | DISCUSSION

The effect sizes of AIT as demonstrated in trials for AR depend on the validity of definitions of, that is, the pollen season (PS) start and end as well as the peak pollen period (PPP).[13,15] The pollen flight is influenced by the characteristics and the profile of the flowering season, which are affected by local environment and climate. Pollen concentration also depends (a) on the pollen type: grass pollen, for example, disperses less efficiently by wind than birch pollen [23] and (b) on the size of the geographic area addressed (eg, the Rhône-Alps region in France is bigger than the Pannonian lowlands region in Austria, with 14 vs 3 pollen monitoring sites being included in the analysis). For this reason, pollen load over a geographical area might be less homogenous, resulting in weaker correlation between symptoms and pollen concentrations. Consequently, any definition should always consider local conditions.[13] Therefore, we evaluated the accuracy of the recently published EAACI definition of pollen season and pollen exposure times[15] of various European geographic regions and yearly changing of pollen concentrations. This analysis will put scientific ground for its application in future trials, for example, in AIT field studies and clinical routine.

In the frame of this analysis in three European regions and our recently published report of German data,[18] we could confirm that the EAACI criteria lead to the identification of PS for all areas in subsequent years for birch and grass pollen. In addition, we were able to demonstrate that (a) the TNSMS is correlated with birch and grass pollen levels within the respective pollen seasons (with the exception of grass pollen in 2016 for Finland and France, for which correlation coefficients are not statistically significant; for the latter, however, the symptoms of users in the beginning of September in France may be influenced by, e.g., local ragweed (*Ambrosia*) pollen) and (b) the maximum symptom levels occurred mostly within the PPP following the EAACI criteria.[15] This current calculation also underlines the feasibility of the criteria to serve as the basis for clinical trials in the future such as confirmatory field-based trials in AIT and for management of AR patients in the clinical routine. Based on our findings, the EAACI definitions for birch and grass are scientifically justified and sound for practical use. However, additional analyses on further European regions on a sufficient number of PHD users may also be required to account for local conditions and deviations.

Since PHD does not collect pollen-specific symptoms, it is obvious that the symptom levels are high not only within the pollen season of aforementioned pollen types, but also apart from it, thus indicating the influence of additional parameters that affect the scores reported by PHD users. First, the flight of, for example, the birch pollen in many regions is preceded by the flight of hazel (*Corylus*) and alder (*Alnus*) pollen, which also possess analogue structures of the major allergen Bet v 1. This will lead to an immunological "priming" of the poly-allergic patients. This phenomenon has been shown in birch-allergic subjects experimentally in nasal provocation tests with the same birch pollen doses before and after birch pollen exposure. The above-mentioned structures of Bet v 1 in hazel and alder pollen may have the same effect of the priming as a birch pollen season itself.[24] Repeated daily exposures to pollen allergens modify the mucosal inflammatory cell profile and in particular promotes the epithelial accumulation of effector cells—which may explain high symptoms at the beginning of the birch pollen flight in subjects who have been exposed already to hazel and alder with Bet v 1 similar allergens.[25]

Secondly, there can be a co-seasonal pollination of other source allergens as in regions in France during the beginning of September with a natural coincidence of the grass and ragweed pollen (*Ambrosia*) flight. Also, the analysis of the region in Finland confirmed a local maximum around the beginning of April for all 3 years, again indicating that a seasonal aeroallergen (local alder [*Alnus*] pollen season) plus possible pollen resuspension (eg, due to snow melting and road surface de-icing) may be the cause of this event. Overall, the number of users and the TNSMS in all country regions and years under investigation remarkably concur with the pollen season period, suggesting that the former can be considered as a proxy of symptom level, while strengthening the effectiveness of the EAACI criteria for the PS definition for AIT and clinical practice support.

Evaluation of the criteria over several years demonstrated stability of their performance—except for the low birch season of 2015 in Finland (Table S4a). In that year, TNSMS were not correlated with the birch pollen concentrations at all. An evident explanation is that during that year, the birch pollen concentration was not sufficient to induce the allergy symptoms above the noise level caused by other pollen and non–pollen-related factors. As a result, this season was not suitable for birch-related clinical trials in Finland. Noteworthy, the absolute concentrations in 2015 in Finland were not small if compared with other geographical regions (Table S2a-c). But they were several times lower than those in Finland during other years. This observation highlights the regional differences in population sensitivity to pollen concentrations: Tolerance to birch pollen concentrations in Finland is much higher than in Central Europe. The current season definition does not account for this variability.

One limitation of our analysis is the limited number of experienced sites involved as well as the limited amount of datasets from patients who had to fulfill (pre-specified) inclusion criteria for reporting. However, the high correlation of symptom levels reported by PHD users with pollen concentration levels in our current analysis (as well as in our recent report [18]) indeed indicates that the aforementioned symptom reporting is an adequate proxy of actual, clinically justified and valid measure of (clinically relevant) symptom severity.

Finally, it should be emphasized that the EAACI criteria are tentative and should always be evaluated with the aid of (prospectively reported) actual symptom data as bioregional and environmental factors indeed affect local thresholds for allergy-inducing pollen concentration levels.[15] On this basis, it can be expected that for specific geographical regions in Europe the EAACI criteria may not always lead to the definition of a pollen season, as already suggested by Karatzas et al.[26] for the case of Olive *(Olea)* (and to some extend of cypress [*Cupressus*]) in a Mediterranean country (Greece). However, the results presented in this study and the previous study from Germany [18] clearly demonstrate the EAACI definitions for birch and grass to be effective and feasible in the four countries analyzed. Further work of the Task Force group will aim to reproduce this finding in other European regions.

5 | CONCLUSIONS

The level of airborne pollen in the atmosphere is influenced by local environmental and climatological factors which dictate the flowering phenology of species releasing pollen causing allergy. This poses a challenge in the effective definition of criteria for the identification of pollen season start and pollen season end, as well as for the identification of the peak pollen period. In a recently published Position Paper, a Task Force of experts of the European Academy of Allergy and Clinical Immunology (EAACI) comprising both aerobiologists and clinicians defined criteria for clinical relevant pollen "seasons" for a variety of plant species. To confirm these definitions, we have analyzed reported symptom and used medication data from the patient's hay-fever diary (PHD) and birch and grass pollen concentrations in Germany in a previous research and have found a positive and significant correlation and therefore a confirmation of the EAACI criteria on the regional level. In the subsequent analysis reported here, we have further investigated three additional European regions (in Austria, in Finland, and in France) again for three subsequent years.

In conclusion, we identified the pollen season characteristics and we also confirmed a sound correlation between TNSMS and birch and grass pollen season start, end, and peak pollen period in all three European regions. Based on the current analysis and the previous research, the validity of the EAACI definitions on birch and grass pollen season and for a variety of geographical locations is consistently confirmed. Their clinical use in future clinical trials on AIT as well as in daily clinical routine for optimal patient care is recommended.

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CONFLICT OF INTEREST

Dr Karatzas reports personal fees from EAACI, during the conduct of the study. Dr Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding BV/HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Nuvo, grants from Circassia, grants and personal fees from ASIT Biotech Tools SA, grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis SA, personal fees from Mobile Chamber Experts (a GA^{2}LEN Partner), personal fees from Indoor Biotechnologies, grants from Glaxo Smith Kline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from Novartis, personal fees from ROXALL, all outside the submitted work. All other authors have nothing to disclose.

AUTHOR CONTRIBUTIONS

K.Bastl and U.Berger provided the correlation data from Austria (through the Austrian Aerobiology Network, see acknowledgments). M.Thibaudon provided the correlation data from France (through the French Aerobiology Network, see acknowledgments). M. Sofiev provided the correlation data from Finland (through the PS4A project of the Academy of Finland (Grant nbr 318194). K.Karatzas (KK) made the statistical analysis of all data analyzed and provided the first draft of this report. O.Pfaar (OP) and K.C.Bergmann (KCB) reviewed and revised the first draft where applicable. B. Werchan, OP, KK, and CB prefinalized the article in a working-group meeting. As members of the EAACI Task Force initiative, all co-authors contributed to this work from this draft stage by critical review and evaluation. All authors have given their final approval for submission of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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