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Development of the EAACI% season definition a backup for a global application

To the Editor,

Pollen seasons progress differently in their timing, course, and intensity in different countries/biogeographical regions depending on regional factors such as vegetation, elevation, urbanization, and others. The variable regional situation often provides obstacles for a standard season definition.[1] The season definition of the European Academy of Allergy and Clinical Immunology (EAACI) was published as a pollen concentration season definition depending on the selected pollen type reaching a certain threshold after a certain period of consecutive days,[2,3] and it was demonstrated that they can be correlated with pollen-induced symptom loads.[4] The season definition was developed for studies with a medical framework, particularly to allow a prospective approach. However, pollen concentrations do not reach the same level in Europe or globally and affect persons concerned differently.[5] Therefore, there is a strong need to expand the scope of application of the EAACI season definition to a retrospective approach if the standard season definition criteria are not met within the site selection or during a clinical trial.

Hence, we tried to transfer the EAACI season definition criteria into a percentage definition (EAACI%) for birch and grasses in a first approach herein to include areas where the pollen concentrations do not meet the criteria of the EAACI season definition or small gaps in the data record prevent an EAACI season definition result. For this

TABLE 1 Calculated thresholds of the EAACI% definition for birch ($v_{b,s}$) and grasses ($v_{g,s}$) for the start of the main pollen season ($v_{a,1}$), the end of the main pollen season ($v_{a,2}$), the start of the peak pollen season ($v_{a,3}$), and the end of the peak pollen season ($v_{a,4}$)

	Main season start ($v_{a,1}$)	Main season end ($v_{a,2}$)	Peak season start ($v_{a,3}$)	Peak season end ($v_{a,4}$)
Birch ($v_{b,s}$)	$v_{b,1}=0.013$ 2 (1–2 days)	$v_{b,2}=0.968$ 6.4 (2–10 days)	$v_{b,3}=0.081$ 1.8 (1–3 days)	$v_{b,4}=0.868$ 3.1 (1–5 days)
Grass ($v_{g,s}$)	$v_{g,1}=0.016$ 4.7 (2–6 days)	$v_{g,2}=0.962$ 13.2 (5–21 days)	$v_{g,3}=0.182$ 3.6 (1–7 days)	$v_{g,4}=0.683$ 7.4 (2–13 days)

Note: In addition, the mean absolute deviation for all stations and years as a comparison to the standard EAACI season definition is displayed, including the 25% and 75% quantiles in brackets.

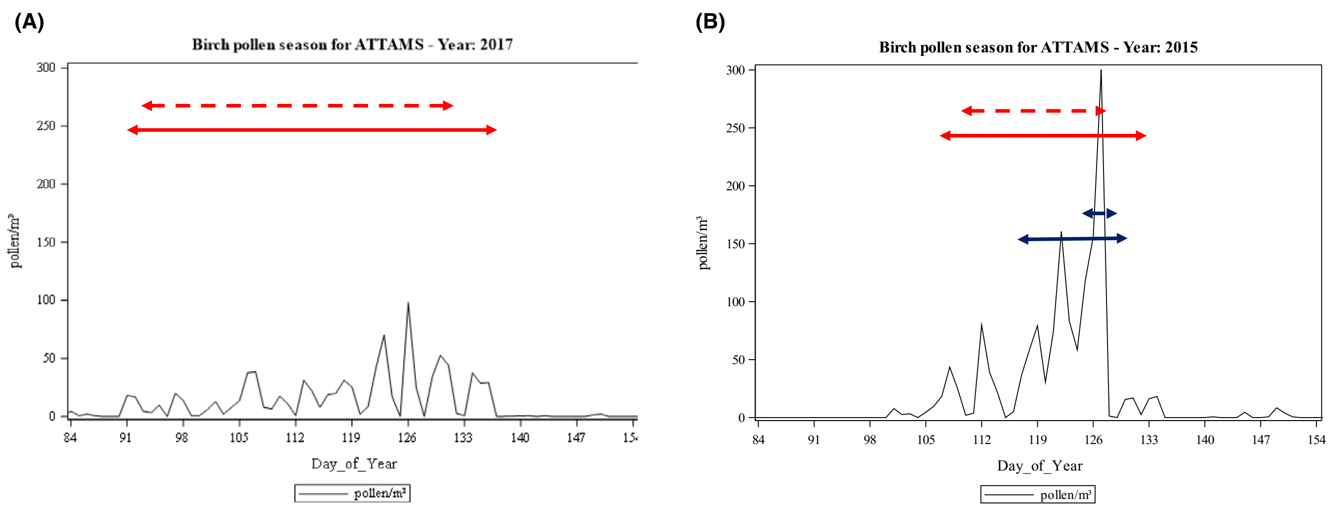

FIGURE 1 Course of the birch pollen season of the station Tamsweg (Austria) for the years 2015 and 2017. (A) Neither the main pollen season, nor the peak pollen season could be derived from the EAACI definition (no matching criteria), but only from EAACI% definition. (B) Both season definitions could be applied. The solid lines display the start and the end of the main pollen season and dashed lines the peak pollen season. The blue lines show the ranges of the EAACI season definition whereas the red lines display the ranges of the EAACI% definition

"backup" season definition, ten pollen monitoring stations across central and eastern Europe were used as the calculation basis for transforming the EAACI season definition.

A cumulative relative pollen concentration (r_d) was calculated for the start, end and peak days of the standard EAACI season definition applying the following formula:

$r_d = \frac{\sum_{i=1}^{d} p_i}{\sum_{i=1}^{365} p_i}$. Summarized, the cumulative pollen concentration (p_i) from the first day of the year to day d is divided by the yearly total sum of the respective pollen type.

For further optimization, these values were calculated for all sites, pollen types, and years to minimize the mean absolute deviation in comparison with the standard EAACI definition.

This calculation results in four percentage values (v) per pollen type, which define the start and the end of the (peak) pollen season. If the relative cumulative pollen concentration exceeds one of the thresholds (v), the respective date marks the (peak) pollen season start/end of the EAACI% definition. For the result validation, the difference in the season's duration was compared with each of the definitions applied (Table 1).

Additional information regarding the methodology and results as well as a calculation example can be found in the Appendix S1. To evaluate the EAACI% season definition, the Austrian pollen monitoring site of Tamsweg (ATTAMS) was selected as an experimental station to compare both season definitions and to test the application to data, where the EAACI season definition fails (Figure 1).

This first attempt demonstrates that the EAACI season definition criteria could successfully be converted into a percentage definition. We recommend using the herein described EAACI% season definition for predictive assistance in site selection or retrospective analysis in sites/countries where the EAACI season definition could not be applied during an ongoing trial. This transformed definition allows an accurate assessment of the pollen season using EAACI criteria in terms of start and end of the pollen season where the EAACI season definition would fail. A moving average season definition usually used in trend analysis, could improve the results of this definition in the future approaches.[6] Taking together this calculation may be helpful in trial regions of interest with low pollen concentrations, an exceptional less intense season, or other possible obstacles for pollen concentration-based season definitions. However, further validation with clinical data from hayfever patients is needed.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Gender-specific decline in perioperative allergic reactions in Norway after withdrawal of pholcodine

To the Editor,

There is a known gender difference in immunological diseases. Women are overrepresented both during fertile years and to a lesser degree before menarche and after menopause, suggesting both genetic and hormonal mechanisms.[1]

Perioperative allergy and anaphylaxis are rare events and, therefore, challenging to study. In the recent NAP6 studies, the incidence of a severe perioperative reaction is estimated to be 1 in 10 000, and the authors suspected a higher true incidence based on some incomplete case reports not included in their work.[1,2] Mertes et al.[3,4] have demonstrated a female predominance, and Florvaag et al.[5] hypothesize possible cross-sensitization with quaternary ammonium ion-containing compounds and the use of such compounds in cosmetics, as a possible explanation. The Norwegian Network for Anaphylaxis under Anesthesia (NARA) has published several studies describing perioperative hypersensitivity reactions in Norway. The effect of the withdrawal of a pholcodine containing cough syrup was evident, with a significant decline in the number of reports and IgE sensitization from 2007 to 2009.[6] The purpose of this study was to investigate the influence of gender on the decline in perioperative hypersensitivity reports.

We analyzed 1,379 reports from 1997 to 2017, based on standardized reports of patient characteristics, clinical presentation, and laboratory investigations. Severity of the reaction was for additional analyses converted into "Mild" (1–2) and "Severe" (3–5) based on a modified Ring and Messmer scale. Age-group splits were constructed according to the Norwegian national average age of menarche at 13 years and menopause at 51 years.

Of the 1,379 reported cases, 461 were men and 918 were women. Median age was 42 years (range 0–89 years). Muscle relaxants were used in 1,023 patients (74.2%). There was a female predominance in all age-groups but more pronounced in women of 14 to 51 years old. There was no significant difference in reaction severity between men and women, men being reported with 51.2% "Mild" reaction and 40.8% "Severe" (remainder missing), while in women 49.2% had a "Mild" and 42.4% had a "Severe" reaction ($p = .52$).

There was no clinically relevant gender difference in the increase in serum tryptase for the different grades of severity (Table 1).

From 1997 to 2007, there was a mean of 76 reports per year, and after an initial yearly increase in number of reports following the establishment of the registry, there was a mean of 87 yearly reports from 2001 to 2007. After 2007, the mean number of reports fell to 61, with stable reporting from 2009. There was no change in the case-reporting procedures during the timeframe of this study. The gender difference was significant in both periods of stable reporting. From 2001 to 2007, there was a 72% female predominance ($p < .01$), and from 2009 to 2017, 60% were women ($p < .01$) (Figure 1).

The allergic phenotype is influenced by sex hormones, where estrogen acts as both anti- and pro-inflammatory, while testosterone and progesterone are anti-inflammatory.[7–14] Finding a female