

RESEARCH LETTER

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Seasonal variation in total and pollen-specific immunoglobulin E levels in the European Community Respiratory Health Survey

To the Editor,

Several small-scale studies limited to allergic patients have reported higher IgE sensitization rates or higher specific IgE (sIgE) level to pollens during or following the pollen season compared to out of pollen season.^{1–4} However, to the best of our knowledge, such studies have not been conducted in larger, more representative populations. Evidence shows that climate change may lead to changes in the pollen seasons for both grass and birch (earlier start and higher counts)⁵ but the likely impact of such changes on sensitization to these pollens is unknown.

This analysis provides some indirect information on the potential impact of changes in pollen levels on serum markers of allergy in the general population. We examined seasonality of total and pollen-specific (Timothy grass and birch) sIgE levels in blood samples taken on one occasion from 13673 participants aged 20–44 years from 35 centres in 15 countries (Australia, Belgium, France, Germany, Iceland, Ireland, Italy, New Zealand, the Netherlands, Norway, Spain, Sweden, Switzerland, UK and USA) enrolled in the European Community Respiratory Health Survey from 1991–3.⁶ The lower limit of detection of the assay used for sIgE was 0.35 kU/L. Seasonality was examined by comparing the expected IgE levels in blood samples that were taken in spring, summer and autumn to that in winter using gamma generalized linear models (GLM) and tobit models with adjustment for age and sex. Season was defined on a 3-month basis (eg spring was March–May in northern hemisphere and September–November in southern hemisphere). Country-level estimates were pooled to obtain regional estimates using random effect meta-analysis. Four regions (Australasia, Northern Europe (NE), Southern Europe (SE) and the USA) were considered for total and grass-specific IgE. Birch-specific IgE was pooled from seven European countries (Belgium, Germany, Norway, the Netherlands, Sweden, UK and Switzerland). Our analyses assessed whether IgE levels were higher in those tested during spring or summer or in the probable pollen seasons compared to winter for each country based on literature. Ethical permission for each centre was granted by local ethics committees, and all participants signed informed consent.

When there was sufficient data, we repeated the GLMs using bi-monthly periods (Jan/Feb, Mar/April etc). We further adjusted GLMs for self-reported allergies in sensitivity analysis to account for any

differences in proportion of allergic participants included in each season and applied logistic regression models to examine the seasonal variations of proportion of participants sensitized to grass and birch and proportion of participants reporting allergies. Interaction between season and self-reported allergies was examined.

The overall prevalence of sensitization was 19.4% for grass pollen ($n = 13,669$) and 11.2% for birch pollen ($n = 8840$). Overall, 32.7% self-reported a history of asthma, nasal or skin allergy ($n = 12,462$). Two countries, Iceland and Ireland, were excluded from sIgE analysis due to data sparsity.

There was little evidence that those with allergic diseases were more likely to have their blood samples taken at a particular time of year (data not shown).

There was no significant variation in total IgE or pollen-specific IgE by season overall (Figure 1). However, the pattern of pollen-specific IgE in some regions was consistent with previous reports of increases during or after the relevant pollen season. The sIgE level to grass pollen was significantly higher in those tested in spring and autumn compared to winter in SE, but not in NE, Australasia or USA. The ratio of expected sIgE level to grass pollen in SE was 1.55 (95% CI 1.09, 2.21) in spring and was 1.49 (95% CI 1.06, 2.09) in autumn. Pooled sIgE to birch pollen was higher in spring than other seasons, although not reaching conventional level of statistical significance—ratio 1.45 (95% CI 0.94, 2.26). In the 15 countries included, only USA (which had only one centre) showed higher total IgE level in summer compared to winter (Figure 1a).

Bi-monthly analysis (Norway excluded due to data sparsity) showed more convincing seasonality (Figure 2). In SE, increased grass pollen sIgE was seen in May/June with ratio 1.68 (95% CI 1.09, 2.61) compared with Jan/Feb (Figure 2a). Increased IgE levels to grass pollen were also seen during June/Aug (vs. Jan/Feb) in NE (Figure 2a) and during Jan/Feb (vs. July/Aug) in Australasia (data not shown), although conventional levels of statistical significance were not reached. In the six countries with relevant data, birch pollen sIgE was higher in May/June than in Jan/Feb with a ratio of 1.96 (95% CI 1.23, 3.11) (Figure 2b).

All seasonal associations were little altered by further adjustment for history of allergies or by use of tobit models (data not shown). There was no consistent evidence of greater seasonality in those with and without self-reported allergies (data not shown).

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Although the statistical significance of associations reported here varies, overall the data are consistent with the hypothesis that sIgE to grass and birch pollen is higher during or in the month after the relevant pollen season. We did not identify any convincing evidence that total IgE levels change by season or month. This is consistent with findings of some but not all previous small studies. A panel study of 17 allergic rhinitis/asthma patients in Germany reported an increase in geometric mean sIgE level to grass during the grass pollen season.⁴ However, a panel study of 15 seasonal allergic rhinitis and/or asthma patients in Turkey found

Key Messages

- Previous work in populations found higher specific IgE levels in the relevant pollen season.
- We evaluated total and pollen-specific IgE levels in a cross-sectional survey of 13,673 adults.
- Our data support the concept that pollen-specific IgE increases during the relevant season.

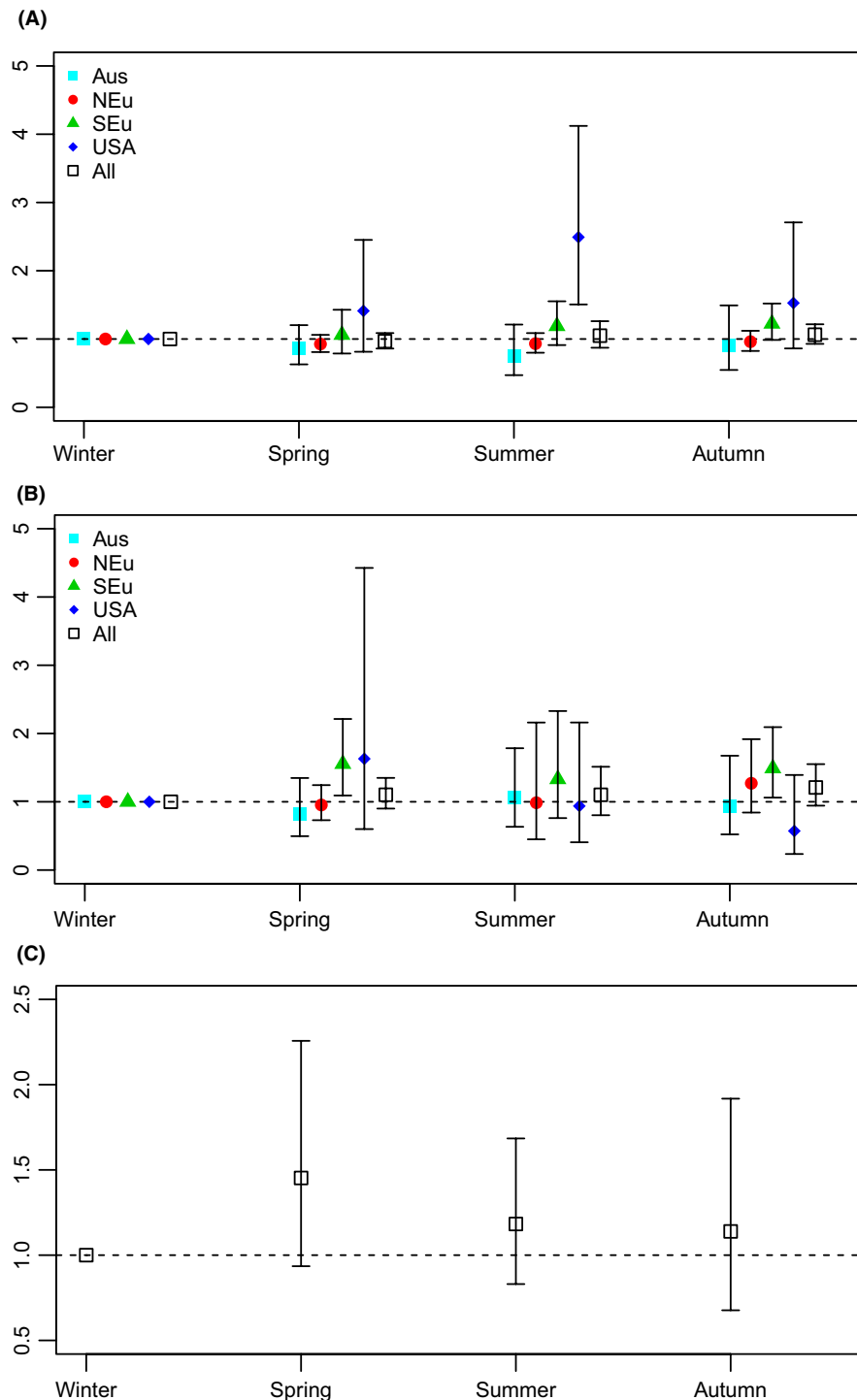
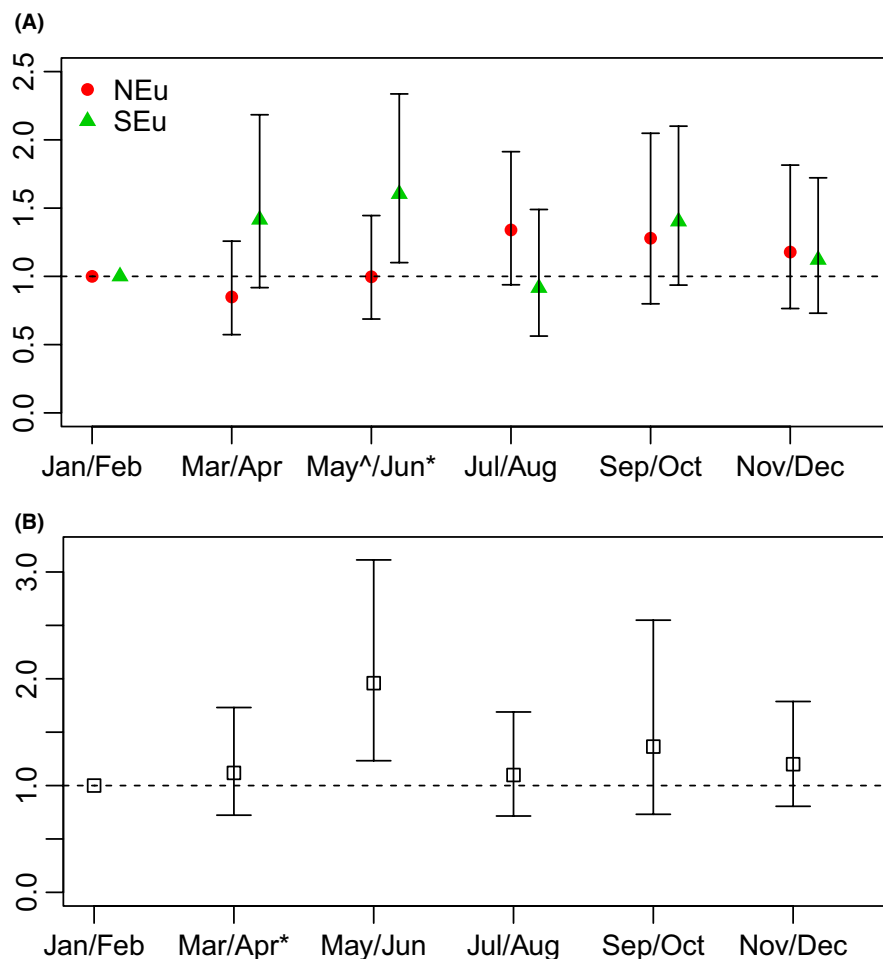


FIGURE 1 Ratio of expected IgE level by season in comparison to winter. A, total IgE level, B, sIgE level to Timothy grass pollen and C, sIgE level to birch pollen. Regional and overall-pooled result from GLMs with the adjustment of age and sex. Remarks: Aus: Australasia. NEu: Northern Europe. SEu: Southern Europe

FIGURE 2 Ratio of expected IgE level by bimonthly period in comparison to Jan/Feb. A, sIgE level to Timothy grass pollen and B, sIgE level to birch pollen. Result from GLMs with the adjustment of age and sex. Remarks: NEu: Northern Europe. SEu: Southern Europe. In A, * marks the probable peak grass pollen month in Northern Europe and ^ marks Southern Europe's. In B, * marks the probable peak birch pollen month in the study countries



no significant changes in their monthly skin prick test reactivity to grass over a 12-month period.¹ Small panel studies conducted among apple-allergic patients in Copenhagen ($n = 26$)⁷ and among birch-allergic seasonal rhinitis patients in Sweden ($n = 28$)³ both reported significant increases in serum sIgE level to birch during the birch pollen season.

It is uncertain why the sIgE level to grass was higher in autumn than in winter in SE. A small panel study among seasonal rhinitis patients in the United States ($n = 30$) showed skin reactivity to tree pollen was highest in October, a non-tree pollen season, in comparison to February, July and August² but we did not see any seasonality in the small number of people in our data set ($n = 114$) studied in the USA.

Studies examining seasonal variation in total IgE are limited. They mostly focussed on those with symptomatic allergies and were usually small in scale. One study of 17 patients with allergic rhinitis/asthma found significantly higher total IgE level during the grass pollen season⁴ but another study of 47 patients with severe asthma showed little seasonal variation.⁸ Perhaps, the negative result for total IgE is unsurprising as total IgE likely reflects reactivity to all allergens, each with different seasonal patterns. The higher level seen in summer months in the single centre in USA (Portland) may reflect other regional pollen seasons that were not considered in this study, for example, ragweed.

Our large and geographically diverse study has limitations when used to explore seasonality of markers of allergy. Our analysis is based on blood testing of different individuals on one occasion, rather than repeated measures on the same person on several occasions during the year. Complex data distributions and censored data may reduce the accuracy of seasonality estimation. The small number of people tested in some countries in some months may compromise statistical power, especially in the sIgE analysis. We were unable to link our data to actual pollen levels as these are unavailable at scale for the period of study (1991–93). Unexpected variations of IgE levels may be related to variations in actual pollen exposures among participants during the same season, the actual period of pollen seasons and other seasonal confounders, for example, meteorological factors.

Despite these limitations, our data suggest that expected levels of sIgE to grass and birch pollen rose by 45–55% in spring compared to winter. The clinical significance of this level of change in sIgE level is uncertain although we know that higher sIgE levels to grass were associated with a higher frequency of reporting symptoms on exposure to pollen,⁹ and seasonal variations in allergic disease are well described.

Our work suggests that seasonal variations in sIgE levels may be exaggerated in warmer climates (the warmer Southern parts of Europe show greater seasonal variation in sIgE levels). The extent to which global warming affects this seasonal variation in different climatic regions remains unknown.

In conclusion, we examined the seasonality of sIgE level to grass and birch pollens and total IgE level in general adult populations using data from a cross-sectional multinational study. Evidence of seasonal variation of sIgE to both pollens—with higher levels in spring, and potentially higher levels in summer, than winter—is demonstrated at the regional level. Future research using sIgE level, for birch in particular, should consider adjusting for season. Panel studies with precise exposure assessment, repeated measurements of allergic markers and symptoms, and carefully considered sample size would help to refine the findings in this study.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The authors roles were as follows: HL: conceptualization, methodology, investigation, writing – original draft and visualization; DJ: conceptualization, methodology, investigation, writing – review and editing, funding acquisition and supervision.

ETHICAL APPROVAL

Alfred Hospital Ethics Review Committee 24 / 91; Comité Consultatif National d'Ethique Pour les Sciences de la Vie et de la Santé, Section Technique, N/réf.AB/GM/91-298 - 19/07/91; INSERM- Biomedical research authorization n°91020 (01/03/91), Approval of the Commission Nationale Informatique et Liberté (CNIL (protection of the data) 05/08/91; Ethikkommission der Ärztekammer Schleswig-Holstein, Positive Votum; Ethikkommission der Medizinischen Akademie Erfurt, Positive Votum; The Regional Committee for Medical and Health Research Ethics West Norway Approval number: 42.91; Regional Ethical Review Board in Uppsala. 1990/257 and 1991/33; Ipswich District Hospital Ethics Committee; Norfolk and Norwich Hospital Ethics Committee.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study may be available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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