Clinical Communication

Title: Seasonality of food-related anaphylaxis admissions and associations with temperature and pollen levels

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The authors declare that they have no conflict of interest.

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Clinical implications and importance

This is the first quantification of seasonality of food-related anaphylaxis admissions. Risk of food-related anaphylaxis admissions were higher around June in England (22% higher vs. January), especially among children below 15 years old. Healthcare professionals should consider this in managing patients at risk of food-related anaphylaxis.

Keywords:

Food-related anaphylaxis; hospital admissions; seasonality; temperature; pollen; time series
Food-related anaphylaxis may be associated with seasonal ambient exposures, such as temperature and pollen. To date, state of the art statistical techniques for identifying seasonal trends and potential associations with ambient exposures have not been applied to the available data. Here, using time series analysis, we assess seasonality in food-related anaphylaxis hospitalisations in England, to determine whether there is any association with ambient temperature and pollen exposure.

We obtained monthly counts of food-related anaphylaxis hospital admissions (T78.0) in England, and central England mean monthly temperature and calculated average monthly pollen count for 2010-2018. Admission and temperature (but not pollen) data were also available for 1998-2010. We used Poisson generalized additive models for time-series to examine seasonality of admissions and the association of admissions with monthly mean temperature and pollen (exposure in the same and the previous month) from 2010-2018 (Methods and materials, Online Repository). Seasonality of admission and the temperature-admission associations were also examined in the extended data from 1998-2018.

From 2010-2018, there were 15405 hospital admissions for food-related anaphylaxis (25903 from 1998-2018) (Table E1, Online Repository). There was a seasonal trend in admission (Figure 1) with a peak in June (Relative risk (RR) 1.22 95% Confidence Interval (CI) 1.13, 1.32 compared to January). In children under 15 years, this peak was particularly marked (RR 1.39 95%CI 1.26-1.54 compared to January), but it was less apparent in young adults (RR 1.14 (95% CI 1.05, 1.25)) and not present in adults over 45 years (1.01 (95% CI (0.95, 1.07)). This pattern was also seen when evaluating all available admissions data (1998-2018) (Figure E1, Online Repository).

We compared the admission risks between exposure levels at the 95th and 5th percentile. There was increased risks of admissions for *Ambrosia* (same month mean; RR 1.16 95%CI 1.03-1.31) and *Quercus* (same month mean; RR 1.12 95%CI 1.04-1.21) and, when a lag was considered, for *Fraxinus* (lagged one month mean; RR 1.05 95%CI 1.01-1.10) (Figure 2). Unexpectedly we observed a significant decreased risk for same month levels of *Fraxinus* (same month mean RR 0.94 95%CI 0.88, 0.99), *Poaceae* (same month mean; RR 0.86 95%CI 0.77-0.96) and *Urtica* (same month mean; RR 0.85 95%CI 0.77-0.94). Of the 11 pollens we tested, *Betula, Fraxinus, Salix* or *Ulmus* appeared to explain the seasonal peak of admissions in June with a delay effect, as the seasonal peak disappeared when lagged-1-month count of any of these four was included in the model.

There was a non-significant (p > .05) positive association of admission with temperature, (RR 1.07 (95%CI 0.99-1.16) per 10°C increase) from 2010-2018. In the full dataset (1998-2018), this association reached statistically significance (RR 1.10 (95%CI 1.06, 1.14) per 10°C increase). The seasonal peak in June of admissions was noted, even after accounting for temperature.

Our analysis shows seasonality in hospital admissions due to food-related anaphylaxis with a peak around June. This seasonality may be partly related to ingestion of seasonal food and, as suggested in our analysis, the variation in individual pollen levels. Compatible with this, one study in Sweden showed that the number of food-related anaphylaxis events among children allergic to pollens increased during the deciduous tree pollen season. A small study in Japan reported a peak of systemic allergic symptoms due to ingestion of soybean products during and after birch season in adults sensitized to both Bet v 1 and Gly m 4. Certain specific pollens, namely *Fraxinus* (Ash), *Ambrosia* (Ragweed) and *Quercus* (Oak), were associated with higher risk of admissions. Research to date suggests that patients with pollen food allergy syndrome (PFAS) are at lower risk of severe reactions to the causative allergen, so it is unlikely that cross-reactivity between food allergens and seasonal aeroallergens is the main driver of
the seasonal peak observed. However, the above-mentioned report from Japan\(^3\) raises the
possibility that sensitisation to a pollen-homologous food protein component, with or without
primary food sensitisation, can lead to an increased risk of systemic reaction during the pollen
season.

Alternatively, people who are sensitized to aeroallergens have higher level of mast cell density in the
airway \(^5\), and non-specific exposure to aeroallergen may increase their susceptibility to more severe
respiratory symptoms (and therefore admission) on ingestion of food allergens \(^5\). This may be
particularly likely in food-allergic patients with asthma, who often report seasonal exacerbations
during the pollen season. Such a phenomena would not involve cross-reactivity, and thus would not
be limited to foods implicated in PFAS. Higher levels of sensitisation to pollens among the younger
age groups or more recent cohorts \(^6\) might explain the stronger seasonality seen in these groups. Of
note, the more frequent physical activities among children in spring-summer may also contribute to
the summer peak in this age-group.

We have shown that even low-level exposure to *Ambrosia* (ragweed) is associated with increased
food-related anaphylaxis hospitalisations which is of interest in light of likely increases in level of
*Ambrosia* in England due to climate change \(^7\).

Unexpectedly, we found a negative association with a few genera/families (e.g. *Fraxinus*, *Poaceae*).
The underlying reasons are uncertain, but this may be related to an artefact related to the extreme
lack of variation in some pollen levels from June onwards (e.g. *Fraxinus*). *Poaceae* includes pollen of
all grass species. Admissions may have different associations with different grass species. A more
detailed regional and species-specific study would be needed to explore this further.

Although both extreme hot and cold temperatures have been implicated as effect modifiers for food
dependent exercise induced anaphylaxis \(^3,8\), our work does not support strong associations of
temperature with admissions. However, we have only considered monthly mean (rather than daily
temperatures) and this negative finding should be interpreted cautiously. Current laboratory-based
work suggests higher environmental temperatures promote the production and delivery of immune
cells to effector sites while low temperature tends to slow these processes \(^9\). Using daily data with
more personal characteristics of triggers may help refining the temperature-food-related-
anaphylaxis associations.

Our study is the first nationwide study of seasonal trends in food-related anaphylaxis and has used
appropriate time series analysis to examine exposure-outcome associations accounting the year-by-
year increasing number of admissions. However, our hypothesis generating analyses has limitations
including limited data relating to the causes (and potential miscoding) of food-related anaphylaxis
admissions, the crude spatio-temporal scale of the analysis related to confidentiality of data, the
potential inflation of type I error rate due to multiple testing and not adjusting for other pollens or
temperature due to inadequate power. In using a large national dataset, we were unable to link
specific patient episodes to patient-specific clinical data.

In summary, we report seasonality in recorded food-related anaphylaxis admissions in England
which may, in part, be related to pollen exposure. Overall risk of food-related anaphylaxis admission
should be considered higher around June in England, and may indicate a pollen-driven process which
is most relevant to a patients’ risk-profile; it is important for healthcare physicians caring for food-
allergic patients to be aware of this. Analyses based on more refined spatiotemporal scales and with
more clinical detail regarding ingestion of food that triggered the reaction may go someway to clarify
these associations.
Acknowledgements

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Reference


10. Figure legend
Figure 1 Relative risk of food-related anaphylaxis admissions in each month (comparing to January) by age-group, England, 2010-2018. Models were adjusted for yearly trend (y: year old).

Figure 2. Relative risk (RR) of food-related anaphylaxis admissions comparing pollen level at the 95th percentile and 5th percentile by pollen types, England, 2010-2018. Monthly mean and maximum (max.) pollen count in the same month and lagged one month are shown.

Figure E1 Relative risk of food-related anaphylaxis admissions in each month (comparing to January) by age-group, England, 1998-2018. Models were adjusted for yearly trend (y: year old).
RRs – Pollen count at 95th vs. 5th percentile

- Same-month mean count
- Same-month max. count
- Lag-1-month mean count
- Lag-1-month max. count
Table E1 Age and sex distribution of food-related anaphylaxis (ICD10: T780) admissions in England

<table>
<thead>
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<th></th>
<th>N (%)</th>
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<tr>
<td></td>
<td>2010-2018</td>
<td>1998-2018</td>
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</tr>
<tr>
<td>Total</td>
<td>15405</td>
<td>25903</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7827 (50.80%)</td>
<td>13248 (51.14%)</td>
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<tr>
<td>Male</td>
<td>7578 (49.20%)</td>
<td>12655 (48.86%)</td>
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<tr>
<td>Age group</td>
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<tr>
<td>&lt;15</td>
<td>5663 (36.76%)</td>
<td>9425 (36.39%)</td>
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<tr>
<td>15-44</td>
<td>7291 (47.33%)</td>
<td>12014 (46.38%)</td>
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<tr>
<td>45-64</td>
<td>2451(16.91%)</td>
<td>4464 (17.23%)</td>
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</table>
Online repository

**Materials and methods**

**Admissions data**

We obtained monthly data from the Hospital Episodes Statistics (HES) database relating to hospital admissions for England in which food anaphylaxis (anaphylactic reaction due to food, T78.0) was the primary diagnostic code, for the calendar years 1998-2018. HES (coordinated through NHS Digital) collates all hospital admissions data in public hospitals in England.

**Pollen data**

Pollen data were available from January 2010 to September 2018. Monitoring was conducted through the network of pollen monitoring stations run by the UK Met Office in collaboration with the National Pollen and Aerobiology Research Unit in University of Worcester ([https://www.metoffice.gov.uk/binaries/content/assets/metofficegovuk/pdf/data/uk-seasonal-pollen-forecast-datasheet_2019.pdf](https://www.metoffice.gov.uk/binaries/content/assets/metofficegovuk/pdf/data/uk-seasonal-pollen-forecast-datasheet_2019.pdf)). Pollen samples were collected daily or weekly during the pollen season (usually from late March to the beginning of September) using Burkard traps. Genera or family specific pollen counts were made by experts using microscopy.

Daily pollen count data (grains/m³/24 hours) were downloaded from the Medical & Environmental Data Mash-up Infrastructure (MEDMI) database ([https://www.data-mashup.org.uk/](https://www.data-mashup.org.uk/)). These included information from 10 stations in England covering 12 pollen genera/families: Trees - *Alnus* (alder), *Betula* (birch), *Corylus* (hazel), *Fraxinus* (ash), *Platanus* (plane), *Quercus* (oak), *Salix* (willow), *Ulmus* (elm); 'Weeds' - *Ambrosia* (ragweed), *Artemisia* (mugwort), *Urtica* (nettle); and *Poaceae* (all grass).

As admission data were available by month, we generated monthly summary measures of pollen level for each station. These were mean (reflecting the total exposure in a month) and maximum count (indicating the level of extreme exposure in the month). Data from stations which had more than 20% missing records for this period (Chester, Exeter, Cambridge and Worcester) were excluded leaving Ipswich, Leicester, London, Plymouth, Isle of Wight and York. The monthly pollen statistics (mean and maximum) from the six stations were averaged to give monthly levels for England.

(Of note the *Alnus* count data available for March showed relatively high *Alnus*-specific counts suggesting our study period (April to August) did not cover the main *Alnus* season. We therefore excluded *Alnus* from further analysis.)

**Temperature data**

The monthly mean central England temperature (CET) (°C) from 1998-2018 was obtained from the British Atmospheric Data Centre (Met Office Hadley Centre Central England Temperature (HadCET) Series. Available from: NCAS British Atmospheric Data Centre). This temperature time series is representative of temperature fluctuations in the Midlands region of central England, roughly in the triangular region between Bristol, Lancashire and London. The measurements and records were maintained by the Climate Data monitoring section of the Hadley Centre, Met Office. Details of station selections and calculations has been published elsewhere (Parker DE, Legg TP, Folland CK. Parker_etal_IJOC1992_dailyCET.pdf. Int J Climatol. 1992;12:317–42).

**Statistical models**

Poisson generalized additive regression (GAM) models for time series were used to examine the potentially non-linear seasonal trend of food-related anaphylaxis admissions and its associations with temperature and pollen counts. For consistency primary analyses used data for the period 2010...
to 2018 (when admission, temperature and pollen data were all available). In a final step, analyses that required only admissions (or admissions and temperature) data were repeated using information available from 1998-2018.

Firstly, we examined the seasonal trend and the temperature-admission association. Associations between pollen level and admissions were assessed using data between April and August only (data for March and September were sparse with multiple missing data). This is the same approach used by Osborne et al. in a recent pollen-asthma study in London (Osborne NJ, Alcock I, Wheeler BW, Hajat S, Sarran C, Clewlow Y, et al. Pollen exposure and hospitalization due to asthma exacerbations: daily time series in a European city. Int J Biometeorol. 2017;61:1837–48).

To examine seasonal trend, year (2010-2018) and month (January to December) were included as explanatory variables for total monthly admissions. To examine associations of temperature and pollen with admission, monthly temperature and monthly pollen count (for each of the 12 pollen genera/families) were added to the seasonal model separately.

All covariates, including year, month, temperature and pollen counts, were modelled as cubic regression smooth functions s() in gam() using the mgcv() package (Simon N. W. Generalized Additive Models: An Introduction with R. Chapman & Hall; 2006) in R (R Core Team. R. Vienna Austria; 2014. Available from: http://www.r-project.org/). This approach estimates the optimal degree of freedom (k-1), while allowing the user to set the maximum permissible (k). We increased the value of k until the estimated degree of freedom was stable with the minimum general cross validation (GCV) score.

Relative risks (RR) of admission comparing different months (highest risk vs. lowest risk) were reported. As in other studies, and related to the highly skewed distribution of monthly pollen counts, RR for pollen were reported comparing risks at the 95th and 5th percentile of exposure. The RR for temperature were reported per 10°C change for linear association or comparing risks at extremes (95th and 5th percentile) and thresholds, if any.

To examine the possible confounding of temperature on pollen-admission associations, temperature was added to the pollen models. Interactions between pollen counts and temperature were assessed by adding an interaction term using the te() function (mgcv()).

Subgroup analysis by age-group was conducted for seasonal analysis but not in the exposure-outcome analyses due to inadequate power.

Throughout all analyses, exposure in the same month and the previous month were considered.

Delayed effect (lagged effect) longer than one month was not considered in this study due to the potential low statistical power with the use of relatively short and low-resolution time series data (45 monthly records for pollens).