Relationship between pollen concentrations and short-acting β_2-agonist bronchodilator sales in central France: a daily time-series analysis over a 5-year period

To the Editor:

Seasonal asthma may be associated with pollen exposure [1], but the pollens responsible for these exacerbations are not well known. The association between ambient pollen and asthma reflected in emergency department visits and hospitalisations, although studied intensively, has shown inconsistent results [2–4]. In contrast to these infrequent events, short-acting β_2-agonists (SABA) are widely used by patients experiencing increased respiratory symptoms, which translates into increased sales. Respiratory drug sales have been successfully used in ecological studies to illustrate the relationship between asthma and outdoor air pollution [5]. This study is intended to test the relationship between exposure to outdoor pollen in the general population of a continental climate medium-sized town in the centre of France, and SABA sales, over a 5-year period.

Records of all SABA treatments prescribed for people living in the demographically stable Clermont-Ferrand area (France; approximately 285 000 inhabitants) were provided during the study period (2010–2012; 2014–2015) by the French public health insurance database, which covers approximately 80% of the French urban population [6]. Owing to missing data for technical reasons, 2013 was omitted. The health outcome was defined as the number of "cases" per day, whereby a case is defined as the reimbursement of a SABA treatment. For each year of the study period, all individuals receiving at least one reimbursement were identified in the health insurance database from their anonymous registration number. SABA sales for children aged <6 years were excluded because of the uncertainty of asthma diagnosis [1]. This study was entirely anonymous and so approval from the French Ethics Committee was not required. Air pollution (particles with a 50% cut-off aerodynamic diameter of 10 μm, O_3, NO_2), meteorological data and pollen samples (Hirst trap), collected from mid-February to early October, were provided as described previously [6]. 11 pollens were identified (table 1) as were two outdoor molds, *Alternaria* spp. and *Cladosporium* spp., sporulating at the same period as the pollens, as potentially confounding factors. Data on influenza epidemics were obtained from a national network for transmissible disease surveillance. Age and sex were also available from the database.

Data were analysed by overdispersed Poisson regression with generalised additive models (GAMs) [7]. Using non-parametric smoothing functions, GAMs allow flexible control of the effect of trend and seasonal components and of confounding factors whose relationship with asthma is not linear. They can also identify the shape (linear or otherwise) of the curve for every pollen–asthma relationship. The construction of the model began with the introduction of the long-term trend and seasonal variations, using a cubic smoothing spline of the day of the study. Dummy variables of holidays, days of the week and influenza occurrence were then introduced. Quantitative meteorological, pollution and mold variables were introduced as penalised cubic splines with different lags tested. Minimisation of the Akaike criterion

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***Betula*, *Quercus*, *Fraxinus*, *Carpinus* and *Platanus* tree pollens contribute to asthma morbidity and consequent sales of SABA medications in the general population in central France, and *Poaceae*, *Corylus* and *Ambrosia* in some age classes** http://bit.ly/2LWQQVs

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TABLE 1 Relative risk and 95% confidence interval of short-acting β_2-agonist sales for an interquartile increase in pollen concentration across the entire Clermont-Ferrand population, 2010–2012, 2014–2015

Pollen	Lag days	IQR	RR	95% CI
***Fraxinus* spp.**	4	45	**1.08**	**[1.04–1.12]**
***Betula* spp.**	0–5	60	**1.13**	**[1.06–1.20]**
***Carpinus* spp.**	2–5	7	**1.03**	**[1.02–1.05]**
***Quercus* spp.**	1	59	**1.01**	**[1.003–1.025]**
***Platanus* spp.**	0–1	12	**1.15**	**[1.08–1.23]**
***Corylus* spp.**	2–3	40	1.00	[0.94–1.07]
***Alnus* spp.**	0–7	15	1.003	[0.957–1.051]
***Poaceae* spp.**	0–7	43	0.98	[0.93–1.03]
***Plantago* spp.**	0–7	5	0.97	[0.91–1.04]
***Urticaceae* spp.**	1–2	66	1.02	[0.96–1.09]
***Ambrosia* spp.**	3	5	1.05	[0.99–1.11]

Bold indicates significance ($p<0.05$). Lag: associations were estimated for optimal lag defined according to the associations reported for individual lags (*i.e. Poaceae* spp. lag 0–7 corresponds to the mean *Poaceae* concentration from day 0 to day 7).

identifies the most appropriate lag for each variable. Finally, the pollen was introduced in the form of penalised cubic spline, with lags of up to seven days. Lags (single day or mean of several days) were retained after graph inspection. The effect of pollens on asthma in the short term is expressed as a relative risk (RR and 95% CI) for an increase of the interquartile range of grains.

Betula spp., *Fraxinus* spp. and *Quercus* spp. averaged around 70 grains·m^{-3}, with peak levels higher than 1000 grains·m^{-3}, whereas *Platanus* spp. and *Carpinus* spp. averaged only 10 grains·m^{-3} with peak levels around 100 and 200 grains·m^{-3} respectively. The correlation between pollens was low (<0.55). The daily mean±SD SABA sales rose from 46.5±23.6 in 2010 to 59.0±30.0 in 2015. The annual number of people supplied with SABA on at least one occasion increased from 8553 to 9742. Within the entire population, the relative risk of SABA sales associated with an interquartile increase in pollen concentration increased significantly for *Fraxinus* spp., *Betula* spp., *Carpinus* spp., *Platanus* spp. and *Quercus* spp. (table 1). When the influence of age was considered, there were significant positive associations with *Poaceae* spp. 1.05 (1.01–1.09) and *Corylus* spp. 1.08 (1.001–1.17) in 6–14 year-old children and with *Ambrosia* spp. 1.13 (1.01–1.26) in young adults.

Betula spp. is the main pollen-allergen producing tree in Northern Europe. Emergency department visits or hospitalisations for asthma induced by *Betula* spp. pollen have been demonstrated [3, 4, 8]. In contrast to *Betula* spp. (peak levels: 1080 grains·m^{-3}), *Carpinus* spp. counts in our study are low, with peaks of 190 grains·m^{-3}. Only two ecological studies have shown a significant association between *Carpinus* spp. pollen levels and asthma hospitalisations with low mean *Carpinus* spp. levels [4, 9]. *Fraxinus* spp. is widespread in Northern Europe and America. In Europe, high *Fraxinus* spp. pollen levels can reach similar peak levels to *Betula* spp., and both trees co-pollinate in March–April. Only two recent studies have demonstrated a relationship between *Fraxinus* spp. pollens and asthma emergency department visits or hospitalisations in North America [3, 8]. Three studies performed in North America, with peaks exceeding 20 000 grains·m^{-3}, reported associations between *Quercus* spp. pollen and asthma emergency department visits or hospitalisations [2, 3, 8]. Our study is the first to report an association between SABA sales and *Quercus* spp. pollens despite lower peaks (1011 grains·m^{-3}). Associations between exposure to *Platanus* spp. pollen concentrations (peaks >2000 grains·m^{-3}) and asthma were reported in outpatients in Madrid, Spain [10]. In contrast, despite low *Platanus* spp. pollen counts (peak <60 grains·m^{-3}), significant associations have been reported with hospitalisations for asthma in New York City (NY, USA) [3] and with SABA sales in our study.

Significant effect modification by age was observed for *Poaceae* spp., *Corylus* spp. and *Ambrosia* spp. Our study is in accordance with a meta-analysis showing a significant relationship between *Poaceae* spp. pollen and emergency department presentation only in children and adolescents [11], with a Spanish study relating *Corylus* spp. pollen to emergency department visits [12] and with a Hungarian study on the relationship between *Ambrosia* spp. pollen and asthma [13].

The main strength of the present work lies in the study of an extremely large regionally representative dataset comprising subjects of all ages ⩾6 years, living within 15 km of the spore trap. The relationship between drug sales and pollens was examined on the basis of individual taxa. We used appropriate statistical tools to look at the shape of the curve for every pollen spore studied, adjusting for influenza epidemics, molds and outdoor air pollution. The lack of knowledge about pollen sensitisation in our general population should be acknowledged as a limitation. Our population was entirely urban. Pollen effect will vary by climatic region [14]. The lack of association found between pollen exposure and SABA sales in subjects over 65 years supports the argument of SABA sales being mainly for asthmatic and not COPD patients.

In conclusion, using an entire urban population in central France over a 5-year period, our study is the first to support the well-documented relationship between asthma exacerbations, as demonstrated by SABA sales, and *Betula* spp. *Fraxinus* spp. and *Quercus* spp. pollen exposure while also showing relationships with *Platanus* spp. and *Carpinus* spp. pollens despite their low pollen counts. Increased SABA sales were also associated with *Poaceae* spp., *Corylus* spp. and *Ambrosia* spp. in some age classes. Further studies in other geographical areas with different climatic conditions are needed to complement these results.

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