Short-term effect of pollen exposure on antiallergic drug consumption

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Background: Several studies have investigated the association between pollen exposure and asthma emergency admissions, but only 2 have investigated the effect of airborne allergens on consultations for rhinitis or conjunctivitis and none has used drug consumption as the health indicator.

Objective: To analyze the short-term association between pollen exposure and antiallergic drug consumption in the urban area of Clermont-Ferrand, France, taking into account the potentially confounding effect of air pollution and meteorological factors.

Methods: We used the French health insurance database to select all individuals from the Clermont-Ferrand urban area having benefited from reimbursement for antiallergic treatment from January 1, 2000, through December 31, 2001, and from January 1, 2003, through December 31, 2004. An episode of treated allergic rhinitis, rhinosinusitus, or conjunctivitis (ARC) was defined as the association of an oral antihistamine and a local antiallergic drug on the same prescription. The relations between daily changes in pollen concentrations and daily changes in the number of treated ARC cases were analyzed using a Poisson regression model with penalized spline functions.

Results: The risk of treated ARC associated with an interquartile increase in pollen concentration increased significantly for Poaceae (5%, $P < .001$), *Fraxinus* (7%, $P < .001$), *Betula* (7%, $P < .001$), and *Corylus* (2%, $P < .02$). This increase was significant in all age groups for Poaceae and *Fraxinus* pollen and in people younger than 65 years for *Betula* pollen. The effect was mainly concentrated on the present day, except for Poaceae pollens, for which the risk remained significantly ($P < .001$) increased until 3 days lag time.

Conclusions: This study showed a significant increase in treated ARC cases related to Poaceae, *Fraxinus*, and *Betula*. Specific risks are difficult to evaluate for species that share the same pollination period. Time-series studies based on drug consumption are useful to highlight and to supervise pollen-related diseases requiring ambulatory care.

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INTRODUCTION

Allergic rhinitis and conjunctivitis are common disorders with a significant effect on the quality of life.[1] Allergic rhinitis is often associated with asthma, and acute rhinitis episodes are risk factors for asthma exacerbations. In Europe, the prevalence of allergic rhinitis was estimated at approximately 20% among adults.[2,3] Among children in France, hay fever prevalence was 9% in those aged 6 to 7 years and ranged from 11% to 27% among adolescents.[4] Indoor (mite and animal dander) and outdoor (pollen and mold) allergens are often involved in allergic rhinitis, and pollutants (tobacco smoke and urban atmospheric pollutants) exacerbate rhinitis symptoms. Grass pollen is one of the major allergens associated with allergic rhinoconjunctivitis worldwide, but in some regions, birch, cypress, olive, and ragweed pollens also cause concern.

Although the atmospheric pollen counts, as measured by pollen monitoring networks, only imperfectly reflect real individual exposure, allergic symptoms were shown to be correlated with them.[5] Routine pollen monitoring is available in many countries, and the main objective of these networks is to give timely information to physicians and people with pollen allergies. However, the short-term health effect of pollen exposure was evaluated only in a few studies. Most studies[6–10] investigated the association between pollen exposure and emergency visits or hospital admissions for asthma. To our knowledge, only 2 studies[11,12] have focused on the effect of airborne allergens on consultations for rhinitis or conjunctivitis. Data on drug consumption are probably more sensitive for monitoring diseases that essentially involve ambulatory care. The objective of the present study was to analyze the short-term association between pollen exposure and antiallergic drug consumption in the urban area of Clermont-Ferrand, France, taking into account the potentially confounding effect of air pollution and meteorological factors.

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METHODS

Data regarding reimbursements for antiallergic drugs were provided by the French national medical insurance. This health insurance covers all active or retired employees and their dependents and is estimated to cover approximately 80% of the French urban population. It refunds only drugs bought with a medical prescription and, until 2004, antiallergic drugs were not available over the counter. For each year of the study period (January 1, 2000, through December 31, 2001, and January 1, 2003, through December 31, 2004), all the individuals living in the Clermont-Ferrand urban area (approximately 260,000 inhabitants) who had benefited from at least 1 reimbursement for either an oral antihistamine or a local (nasal or ocular) antiallergic treatment were selected via the health insurance database. Within each year, reimbursements were linked up by individuals using an anonymous registration number. For technical reasons, data on drug reimbursements in 2002 could not be used. The analysis was restricted to individuals 5 years and older because diagnosis of allergic rhinitis, rhinosinusitis, or conjunctivitis (ARC) is difficult in young children. An episode of treated ARC was defined as the association of an oral antihistamine drug and of a local (nose or eye) antiallergic drug on the same medical prescription. Population figures provided by the French National Institute for Statistics and Economic Studies were used to calculate the prevalence rates of treated ARC for each calendar year. Because data were extracted from an administrative database and the study did not involve experiments on human subjects, approval from the French ethical committee was not required.

The concentrations in airborne pollen grains were obtained from the national aerobiological surveillance network (Réseau National de Surveillance Aérobiologique). Pollens were collected between February 1 and September 30 of each year using a Burkard volumetric spore trap located in the town center 30 m above ground level. Grass (Poaceae), ash (*Fraxinus*), birch (*Betula*), hazel (*Corylus*), and oak (*Quercus*) pollens were selected for the analysis based on their allergenicity and concentration in the study area.

Mean daily concentrations of pollutants (ozone, black smoke, sulfur dioxide, carbon monoxide, particles, nitrogen dioxide, and nitric oxide) measured at the different urban background stations of Clermont-Ferrand were obtained from the local network on air quality monitoring (ATMO-Auvergne). Meteorological data (minimal and maximal daily temperature and minimal and maximal relative humidity and precipitation) were provided by the national meteorological institute (Météo-France).

The relation between daily changes in pollen concentrations and daily changes in the number of treated ARC cases was analyzed using a Poisson regression model with penalized spline functions allowing for overdispersion.[13,14] A preliminary analysis[15] enabled us to identify maximum daily temperature, minimal daily relative humidity, and mean daily ozone concentration as confounding factors. We also tested for possible confounding time-lag effects of up to 3 days or averaged over 1 to 3 days. The core model included penalized cubic regression spline of time, dummy variables for days of the week and public holidays, penalized cubic regression spline for temperature and relative humidity (using a 2-day average over lags 0 and 1), and penalized cubic regression spline for ozone concentration (lag of 1 day). Diagnostic tools for the models included the partial autocorrelation function of residuals and the Akaike information criterion.[16] The short-term effects of pollen levels were evaluated using independent single-pollen models. In accordance with the physiologic short-term effect of pollen exposure on symptom occurrence, we studied the effect of a 2-day exposure (2-day average over lags 0 and 1). However, because our morbidity indicator reflected the seeking of medical care rather than the first development of symptoms, we also used a polynomial distributed lag model to observe the distribution of the effect over time and to estimate the cumulative effect of up to 6 days (from lag 0 to lag 5).[17,18]

When a significant association was found in the overall analysis (all ages combined), further analyses were performed distinguishing the following age groups: 5 to 14, 15 to 34, 35 to 64, and 65 years and older. Results were expressed as the percentage change (and 95% confidence interval) in the risk of treated ARC associated with a variation in range between the 75th and the 25th percentiles of pollen distribution. Analyses were performed using computer software (MGCV package in R software).[19]

RESULTS

An annual average of 6,780 individuals benefited from the reimbursement of an ARC treatment: 15.9% were aged 5 to 14 years, 33.7% were aged 15 to 34 years, 39.1% were aged 35 to 64 years, and 11.3% were 65 years or older. The overall male-female ratio was 0.8 and was higher among children than among adults (1.4 in children $<$15 years vs 0.7 in individuals $\geq$15 years). The number of treated ARC episodes per person and per year ranged from 1 to 19 (mean, 1.7) (Table 1). Between 2000 and 2004, the yearly number of people having undergone at least 1 ARC treatment increased (from 4,970 to 8,382), and the mean number of ARC treatments per person and per year increased (from 1.59 to 1.77), which led to an important increase over time of the mean number of treated ARC cases per day (from 24.5 in 2000 to 42.1 in 2004, an increase of 65%). The increase in the mean number of treated ARC cases per day concerned the pollination season (between March 1 and July 31) (67%) and the rest of the year (81%). The greatest increase was found for ARC treatments that included nasal corticosteroids: they accounted for 54% of treated ARC cases in 2000 and 62% in 2004.

Assuming an 80% coverage rate of the French national health insurance, the annual prevalence of treated ARC cases increased from 2.8% in 2000 to 4.8% in 2004. The mean annual prevalence of treated ARC cases declined

Table 1. Descriptive Data of Treated ARC Episodes for Individuals 5 Years or Older, Living in the Clermont-Ferrand, France, Urban Area

Variable	Mean (SD)	Percentile distribution								
		Min	5	10	25	50	75	90	95	Max
No. of treated ARC episodes per individual										
2000	1.59 (1.35)	1	1	1	1	1	2	3	4	13
2001	1.65 (1.43)	1	1	1	1	1	2	3	4	19
2003	1.76 (1.59)	1	1	1	1	1	2	3	5	16
2004	1.77 (1.62)	1	1	1	1	1	2	3	5	17
Daily No. of treated ARC episodes										
2000	24.5 (24.3)	0	0	0	10	18	31	55	81	146
2001	31.9 (33.9)	0	0	1	15	24	36	69	100	206
2003	37.7 (32.4)	0	1	2	18	29	54	86	99	186
2004	42.1 (40.5)	0	0	1	21	31	50	96	121	342

Abbreviations: ARC, allergic rhinitis, rhinosinusitis, and conjunctivitis; Max, maximum; Min, minimum.

with increasing age, in particular among males: from 6.2% for males aged 5 to 14 years to 1.6% in males 65 years or older, and from 5.0% to 2.2% in females from the same age groups.

Figure 1 shows the temporal distribution of concentrations in pollen grains and treated ARC cases. Descriptive data on pollen levels are given in Table 2. The median of mean daily ozone concentrations during the study period was 53 $\mu g/m^3$ (range, 0.5–135.5 $\mu g/m^3$), and the medians (ranges) of the maximum daily temperature and minimum daily relative humidity were 17.2°C (−6°C to 40°C) and 49% (10%–97%), respectively.

The relations between daily pollen concentrations and the number of treated ARC cases for all age groups are given in Table 3. The percentage increases of the risk of ARC treatments are presented for a 2-day exposure and for a cumulative exposure of up to 6 days. The risk of treated ARC cases associated with an interquartile increase in pollen concentration was significantly increased for Poaceae, *Fraxinus*, *Betula*, and *Corylus*. For Poaceae and *Fraxinus* pollens, the risk was significantly increased in all age groups (Table 4). For *Betula* pollen, it remained significantly increased only in people younger than 65 years, and for *Corylus* pollen, only in people between 35 and 64 years. The distribution of the risk over time showed that the effect was mainly concentrated on the present day, except for Poaceae pollens, for which the risk remained significantly ($P < .001$) increased until 3 days lag time (Fig 2).

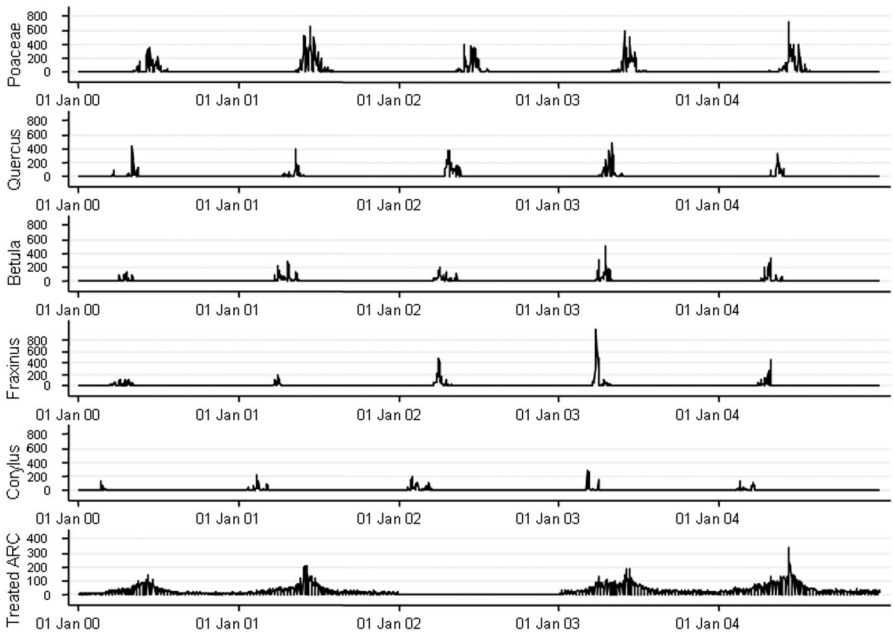


Figure 1. Daily number of treated allergic rhinitis, rhinosinusitus, or conjunctivitis (ARC) cases and daily pollen concentrations (measured in grains per cubic meter), Clermont-Ferrand, France, from January 1, 2000, to December 31, 2004.

Table 2. Descriptive Data on Pollens Levels in Clermont-Ferrand, France, From 2000 to 2004

Type of pollen	No of days[a]	Pollen level[b]	Percentile distribution					
			Min	50	75	90	95	Max
Poaceae	759	22.8 (72.8)	0	0	5	48	165	732
Fraxinus	361	9.3 (51.4)	0	0	0	12	34	975
Betula	369	7.4 (30.8)	0	0	0	10	47	503
Corylus	287	4.0 (19.8)	0	0	0	4	17	295
Quercus	333	8.6 (39.3)	0	0	0	6	45	481

Abbreviations: See Table 1.
[a] Days with pollens levels greater than 0 grains per cubic meter.
[b] Mean (SD) grains per cubic meter.

Table 3. Estimated Percentage Change in the Risk of Treated ARC Cases Associated With a Variation in Range Between p75 and p25 of Pollen Distribution

Type of pollen	No. of days[a]	p75 − p25[b]	% Increase, mean (95% CI)	
			2-d Exposure[c]	6-d Cumulative exposure[d]
Poaceae	759	41	4.8 (3.7 to 6.0)	8.7 (6.9 to 10.5)
Fraxinus	361	33	7.3 (4.6 to 10.1)	12.7 (8.6 to 17.0)
Betula	369	45	7.0 (3.8 to 10.4)	11.0 (5.9 to 16.3)
Corylus	287	23	2.3 (0.4 to 4.3)	2.4 (−0.4 to 5.2)
Quercus	333	47	−0.7 (−2.4 to 1.0)	−3.3 (−6.1 to −0.4)

Abbreviations: ARC, allergic rhinitis, rhinosinusitis, and conjunctivitis; CI, confidence interval; p25, 25th percentile of pollen distribution; p75, 75th percentile of pollen distribution.
[a] Days in the study period with nonzero counts for a given pollen.
[b] Variation in interquartile range of pollen concentration (measured in grains per cubic meter) based on days with nonzero pollen counts during the study period.
[c] $P < .001$ for Poaceae, *Fraxinus*, and *Betula*; $P = .02$ for *Corylus*; and $P = .39$ for *Quercus*.
[d] $P < .001$ for Poaceae, *Fraxinus*, and *Betula*; $P = .09$ for *Corylus*; and $P = .02$ for *Quercus*.

Table 4. Estimated Percentage Increase in the Risk of Treated ARC Cases Associated With a Variation in Range Between p75 and p25 of Pollen Distribution According to Age Group

Type of pollen	% Increase, mean (95% CI) for a 2-d exposure			
	5–14 y[a]	15–34 y[b]	35–64 y[c]	≥65 y[d]
Poaceae	5.7 (3.3 to 8.2)	6.3 (4.6 to 8.0)	3.8 (2.4 to 5.3)	6.4 (4.7 to 8.1)
Fraxinus	7.8 (1.5 to 14.4)	12.5 (7.7 to 17.4)	6.4 (3.1 to 9.8)	5.1 (0.4 to 10.0)
Betula	7.3 (0 to 15.1)	10.0 (4.6 to 15.7)	6.9 (2.8 to 11.1)	5.9 (−0.2 to 12.4)
Corylus	−1.5 (−6.5 to 3.7)	3.3 (−0.2 to 7.0)	2.8 (0.5 to 5.2)	1.9 (−1.7 to 5.6)

Abbreviations: See Table 3.
[a] $P < .001$ for Poaceae, $P = .02$ for *Fraxinus*, $P = .049$ for *Betula*, and $P = .56$ for *Corylus*.
[b] $P < .001$ for Poaceae, *Fraxinus*, and *Betula*; and $P = .07$ for *Corylus*.
[c] $P < .001$ for Poaceae and *Fraxinus*, $P = .001$ for *Betula*, and $P = .02$ for *Corylus*.
[d] $P < .001$ for Poaceae, $P = .03$ for *Fraxinus*, $P = .06$ for *Betula*, and $P = .31$ for *Corylus*.

DISCUSSION

Our study showed a significant increase of the risk of treated ARC cases associated with increases in Poaceae, *Fraxinus*, *Betula*, and *Corylus* pollen concentrations, taking into account air pollution and meteorological factors. Poaceae sensitization was shown to be the major cause of pollen allergy in Europe.[20] In our study, the grass pollination period was associated with a significant increase in antiallergic drug consumption. This risk is obviously underestimated, because allergic people may have begun taking antiallergic drugs before the start of grass pollination or may have bought the drugs before the pollination season. Among tree pollens, *Fraxinus* and *Betula* pollens gave the most consistent results. Although the role of *Fraxinus* pollen in inducing rhinoconjunctivitis has already been described,[21] it has been underestimated because of cross-reactivity among members of the Oleaceae family.[20] In our study, a clear clinical significance of *Fraxinus* pollen exposure was shown. Regarding hazel,

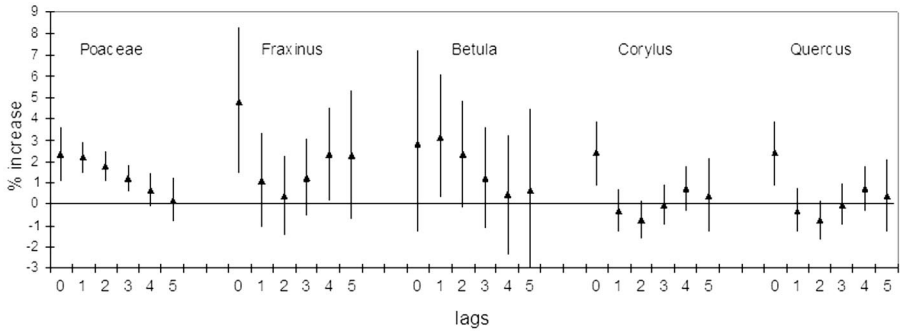


Figure 2. Distribution over time of the increase in the risk of treated allergic rhinitis, rhinosinusitus, or conjunctivitis cases associated with an interquartile increase in pollen concentration (risks estimated with a polynomial distributed lag model).

whose pollination period takes place early in the year (at the end of the winter), only a moderate increase in the risk of treated ARC cases was found, which was significant only in people aged 35 to 64 years. As a consequence of the allergenic cross-reactivity between *Corylus* and *Betula* pollens, *Corylus* pollen can act as a primer for the sensitization of people to *Betula* pollen and clinical symptoms become more marked during the birch pollen season.[20] Furthermore, the diagnosis of seasonal allergic rhinitis may be difficult during the winter when physicians are less aware of the pollen-related allergic risk and viral infections are frequent. Last, at least in some years, hazel pollination may have begun before the start of pollen collection. We did not find any significant increase in the risk of treated ARC cases associated with *Quercus* pollen exposure. Oak pollination occurs after that of other trees, and oak and birch pollens share strong cross-allergenicity.[22] It is, therefore, likely that allergic people sensitized to *Betula* pollen were already under treatment when oak pollination began.

Drug consumption data represent a useful tool for the surveillance of diseases such as ARC, whose management essentially rests on ambulatory care. Based on drug reimbursement data from the French national medical insurance, we estimated an annual prevalence of treated ARC cases of 4%. This figure, which does not include untreated or self-medicated patients, is much lower than the 10% to 20% figure estimated for the prevalence of self-reported symptoms of ARC.[2–4] Furthermore, to improve the specificity of our health indicator, we used a restrictive definition of treated ARC cases (the combination of an oral antihistamine and local antiallergic drugs on the same prescription). It has to be underlined, however, that the differences we observed in the annual prevalence of treated ARC cases according to age and sex are consistent with available epidemiologic data on allergic diseases: prevalence was highest in children and young adults, in males among children and in females among young adults.[1,23] Between 2000 and 2004, we observed a dramatic increase in the number of patients treated for ARC (68%). It is unlikely that an increase in the prevalence of ARC alone could account for such an increase. This increase in treated ARC cases is more likely to reflect changes in medical practices, including higher rates of diagnosis and treatment of mild forms of the disease. Furthermore, greater efficiency and fewer adverse effects have led to a more frequent use of new antihistamine drugs and nasal corticosteroids.[24]

The role of airborne allergens on asthma or rhinitis symptoms is well known. In the International Study of Asthma and Allergies in Childhood, it has been shown that, in Germany, 40% of children were sensitized to pollens but only 12% of children without sensitization had seasonal rhinitis.[25] The health effect of airborne allergen exposure is more difficult to evaluate. Thunderstorms, by increasing the atmospheric concentrations of fungal or grass pollen allergens, have been correlated to emergency visits for asthma.[8,26] Using time-series analyses, some researchers studied the relationship between exposure to air pollutants and outdoor allergens and emergency department visits and hospital admissions for asthma. A positive correlation between pollen levels and emergency department visits for asthma was found in Madrid[10,27] and Canada.[7,9,28] The pollen most frequently involved was grass pollen. Anderson et al[6] did not find any association between hospital admissions and pollen concentrations in London, England, but it is likely that the indicator used (hospital admissions for asthma) was not sensitive enough. To our knowledge, the relationship between pollen exposure and the seeking of health care for less severe acute asthma (without an emergency visit or hospital admission) has not been studied. Cakmak et al[11] found that an increase in ragweed, grass, and tree pollens and fungal spores was associated with an increase in emergency consultations for conjunctivitis or rhinitis in children. Unfortunately, no data on fungal spore exposure were available in our study. Villeneuve et al[12] studied the relationship between outdoor air pollution and visits to physicians for allergic rhinitis among individuals older than 65 years. Although no significant association was observed between air pollution and visits for allergic rhinitis, an increase in ragweed pollens was associated with a significant increase in visits for rhinitis.[12] We also found a significant increase in the risk of treated ARC cases associated with Poaceae and *Fraxinus* pollen exposure among adults older

than 65 years, confirming that pollens can lead to allergic rhinitis in older adults.

We chose to evaluate the effect of pollen, including a fixed predetermined time lag, rather than to select the best single day relation. As recommended by Schwartz,[18] we also investigated the distribution of the effect over time using a polynomial distributed lag model and showed that the effects were concentrated on the present day for tree pollens but remained significant until 3 days lag time in the case of Poaceae pollens.

In conclusion, this study showed a significant increase in antiallergic drug consumption related to short-term exposition to *Fraxinus*, *Betula*, and Poaceae pollens. The estimated risk for *Corylus* pollen was less reliable. The risk associated with each individual species is difficult to ascertain because the trees all shed their pollen in a rather short space of time. Time-series studies based on drug consumption data are nevertheless useful for investigating the effect of pollen exposure on diseases that necessitate mainly ambulatory care.

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