

Short-term effect of pollen exposure on drug consumption for allergic rhinitis and conjunctivitis

Yvon Motreff · Franck Golliot · Michel Calleja ·
Annick Le Pape · Claire Fuhrman ·
Isabelle Farrera · Isabelle Plaisant

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Abstract The aim of the present study was to analyse the short-term relationship between pollen exposure and allergic rhinitis and conjunctivitis (ARC) using drug deliveries in two urban areas in the south of France, from 2004 to 2007. An ARC case was defined as the association of an oral antihistamine drug and a local (nose or eye) antiallergenic drug on the same medical prescription. Generalized additive models and generalized additive distributed lag models, taking into account confounding factors such as meteorological data or days of the week, were computed to estimate the relationship between pollen counts and ARC. This study showed a statistically significant association between pollen concentration in the air and the increase in the number of deliveries in pharmacy for ARC in both urban areas. This

relation was statistically significant in at least one of the two studied cities for *Artemisia*, *Plantaginaceae*, *Poaceae*, *Cupressaceae*, *Quercus*, *Fraxinus*, *Olea*, *Pinus* and *Populus*. In this southern area of France where *Cupressaceae* planting is very developed, relative risks estimated for an interquartile increase in *Cupressaceae* pollen concentration were 1.09 (1.06–1.13) in Montpellier and 1.03 (1.01–1.04) in Nîmes. These results indicate that *Cupressaceae* planting has a population health impact and that alternative needs to be developed.

Keywords Pollen · Drug prescription · Allergic rhinitis · Allergic conjunctivitis · Time series

Y. Motreff (✉) · F. Golliot
Cellule de l'Institut de veille sanitaire en Région
Languedoc-Roussillon, ARS du Languedoc-Roussillon,
28 Parc-Club du Millénaire, 1025 rue Henri Becquerel,
CS 30001, 34067 Montpellier Cedex 2, France
e-mail: y.motreff@invs.sante.fr

Present Address:
Y. Motreff
Département Santé Environnement, Institut de veille
sanitaire, 12 rue du Val d'Osne, 94415 Saint-Maurice,
Cedex, France

M. Calleja · I. Farrera
Montpellier SupAgro, 2 place Pierre Viala, bât 28,
34060 Montpellier Cedex 2, France

A. Le Pape · I. Plaisant
Agence régionale de santé du Languedoc-Roussillon,
28 Parc-Club du Millénaire, 1025 rue Henri Becquerel,
CS 30001, 34067 Montpellier Cedex 2, France

C. Fuhrman
Département des maladies chroniques et des
traumatismes, Institut de veille sanitaire, 12 rue du Val
d'Osne, 94415 Saint-Maurice, Cedex, France

Abbreviations

ARC	Allergic rhinitis and conjunctivitis
GAM	Generalized additive model
RR	Relative risk
CI	Confidence interval

1 Introduction

Allergic rhinitis and conjunctivitis (ARC) affects 16.9–28.5 % of adults in Europe and 24.5 % in France (Bauchau and Durham 2004). ARC impairs quality of life, decreases cognitive functions and can be associated with more severe diseases such as asthma (Bousquet et al. 2001; Marshall et al. 2000).

Grass pollens (Poaceae) are the main cause of allergic rhinitis due to pollens worldwide. However, according to areas and their flora, *Betula*, *Olea*, *Ambrosia* and *Cupressaceae* pollens can cause ARC as well. For example, *Cupressaceae* allergy is a common allergy in the Mediterranean region (Charpin et al. 2005).

Meteorological factors and atmospheric pollution can have an indirect effect on the occurrence of ARC episodes. Indeed, the quantity of pollen grains in the air depends on meteorological parameters such as relative humidity, temperature, wind and precipitations (Breton et al. 2006; Diaz de la Guardia et al. 2006; Laaidi et al. 1997; Stefanic et al. 2005), and atmospheric pollution can exacerbate rhinitis symptoms (Laaidi et al. 2002).

Few studies investigated the association between daily pollen counts and daily episodes of ARC. A Canadian study (Breton et al. 2006) showed a significant relationship between *Ambrosia* pollen counts and over-consultations for ARC. A French study, carried out in Clermont-Ferrand area (Fuhrman et al. 2007), highlighted a significant raise of the risk of ARC associated with an interquartile increase in pollen concentration for *Poaceae*, *Fraxinus* *Betula* and *Corylus*.

The aim of the present study was to analyse the short-term relationship between pollen exposure and ARC using drug delivery in two urban areas in the south of France, from 1 January 2004 to 31 December 2007, taking into account the potentially confounding effect of air pollution and meteorological parameters.

2 Methods

2.1 Studied areas

The study was carried out in two urban areas distant of 50 km in southern France. These two urban areas are composed, respectively, of 6 and 11 cities, each including a major city (Nîmes and Montpellier). Each area is supposed to be homogeneous in terms of air pollution, pollen concentration and meteorology. Analyses were carried out separately for each urban area. Both areas present a Mediterranean climate: dryness with a high sunlight in winter and summer and rain in spring and more important rain in autumn.

2.2 Outcome measures

For each day of the study period (1 January 2004–31 December 2007), all the individuals living in the urban areas of Nîmes (approximately 150,000 inhabitants) and Montpellier (approximately 300,000 inhabitants) who had benefited from at least one reimbursement for either an oral antihistamine or a local (nasal or ocular) antiallergic treatment were selected in the regional database of the French medical insurance. In database, records were linked up using an individual anonymous registration code. The medical insurance covers all active or retired employees and their dependents. In Nîmes and Montpellier, respectively, about 75 and 81 % of the population were covered by this medical insurance during the year of 2007.

The health indicator, further referred to as “ARC cases”, was defined as the association of an oral antihistamine drug and a local (nose or eye) antiallergic drug on the same medical prescription. Children of less than 5 years old were not included in the study because diagnosis of ARC is not very frequent and not very reliable at this age of life.

Because this study was completely anonymous, with aggregated data, approval from the French ethical committee was not required (mail of the *Commission nationale de l'informatique et des libertés—CNIL*—of the 10th of November 2006, file no. 06.412).

2.3 Exposure measures

The daily concentrations in airborne pollen grains were supplied by the French national aerobiological network

(Réseau National de Surveillance Aérobiologique—RNSA). Mean daily airborne pollen grain concentrations were measured during the period using two Hirst spore traps, each one located in the outskirts of town centres of Montpellier and Nîmes. The traps were located 20 m above ground level, and results are expressed as the number of pollen grains per cubic metre of air. Six herbaceous pollens (*Ambrosia*, *Artemisia*, *Chenopodiaceae*, *Plantaginaceae*, *Poaceae* and *Urticaceae*) and height tree pollens (*Castanea*, *Cupressaceae*, *Fraxinus*, *Olea*, *Pinus*, *Platanus*, *Populus* and *Quercus*) were analysed.

2.4 Confounding factors

Mean daily concentrations in pollutants (ozone, nitrogen dioxide, PM_{10}) were obtained from the local network on air quality monitoring (Air Languedoc-Roussillon). Pollutants were measured using 6 urban background monitoring stations, 4 located in Montpellier and 2 in Nîmes. PM_{10} concentration was measured using a Tapered Element Oscillating Microbalance (TEOM). Nitrogen dioxide concentration was determined using a chemiluminescence detector, and the UV photometer was used to analyse ozone concentration. For the three pollutants, concentrations were recorded per hour.

Minimal and maximal daily temperature, minimal and maximal daily relative humidity, quantity and duration of precipitations were provided by the national meteorological institute (Météo-France). The weather station for Montpellier area was located at the Montpellier Méditerranée Airport at 11 km away from the city centre. For Nîmes, the weather station *Nîmes-Garons* was located 13 km away from the city centre.

2.5 Statistical modelling

To study the relationship between daily changes in pollen concentrations and daily changes in the number of ARC cases, we used a generalized additive Poisson regression model with penalized splines (Wood and Augustin 2002) functions allowing for overdispersion (Wood 2006). The Akaike's information criterion (AIC) was used to select relevant variables in the model. Based on the AIC, the 5 following variables were not retained in the final model: means daily

concentrations in ozone, nitrogen dioxide and PM_{10} , and quantity and duration of precipitations.

The final model included penalized cubic regression spline of time, dummy variables for days of the week, public holidays and vacations, penalized cubic regression splines for minimal temperature of the day, penalized cubic regression spline for maximal temperature (using a 4-day average over lags 0 and 3) and penalized cubic regression splines for minimal relative humidity (using a 4-day average over lags 0 and 3). The short-term effect of pollen levels was evaluated using independent single-pollen models. Ozone, NO_x and PM_{10} concentrations were introduced into the initial model, but these factors were not significant and were not kept as confounding factors.

Penalized cubic regression spline of pollen concentration (using a 2-day average over lags 0 and 1) was integrated in the model to study the shape of the relation between pollen concentration and number of ARC cases. This relation was mainly linear but, for some pollens, presented a slowdown from a certain value of pollen concentration. In case of a linear relationship between pollen concentration and number of ARC cases, to estimate a relative risk (RR), pollen concentration was included in the model using a 2-day average over lags 0 and 1. In case of a non-linear relationship, the RR was calculated using a 2-day average over lags 0 and 1 but only for exposures equal or less than the slowdown point, assuming a linear relationship between a concentration of 0 grain of pollen and this slowdown point. In Montpellier, the relations between ARC cases and *Artemisia*, *Poaceae*, *Cupressaceae* and *Olea* presented a slowdown. In Nîmes, this relation was non-linear for *Poaceae*, *Cupressaceae*, *Olea* and *Populus*.

To take into account delay between exposure to pollens, symptoms, consultation and delivery in pharmacy, generalized additive distributed lag models (Schwartz 2000; Zanobetti et al. 2000) were computed as well. The cumulative effect of pollen concentrations on ARC can be calculated with this kind of models. Contrary to generalized additive models (GAM), the shape of the relationship between pollen concentration and ARC is assumed to be linear on the whole exposure range.

Analyses were carried out using R software, version 2.6.2, with the GAM procedure from the MGCV package.

3 Results

3.1 Pollen concentrations

The same pollens were detected in the two areas, but their concentrations in the air were different according to species. Among herbaceous, Plantaginaceae, Poaceae and Urticaceae concentrations were more important in Montpellier than in Nîmes, whereas for the other herbaceous pollens, concentrations were alike. Among tree pollens, concentrations were close for Olea. For the others tree pollens, except for Quercus, concentrations were higher in Montpellier (Table 1). As an illustration of the distribution over time of pollen concentration, Fig. 1a, b shows the pollen distribution over year 2004–2007 for 8 pollens in Montpellier.

3.2 Urban area of Montpellier

From 2004 to 2007, the total number of ARC cases was estimated to be 118,723. Forty-seven percentage occurred among persons aged 15–44 years, 27 % among people from 45 to 64 years, 13 % among children from 5 to 14 years and 12 % among the people aged 65 years and more. Over the 4 years of the study period, an average of 81 cases of ARC was recorded each day. Figure 1 shows the temporal distribution of daily pollen concentrations and number of ARC cases. The median (range) of the minimum

daily temperature, maximum daily temperature and the minimum daily relative humidity were, respectively, 11 °C (–7–25 °C), 20 °C (2–36 °C) and 43 % (9–95 %).

Table 2 shows the RR of ARC for a 2-day exposure and for a 6-day cumulative exposure associated with an interquartile increase in pollen concentration. The positive change in the risk of ARC, associated with a variation equal to an interquartile range of pollen distribution, was statistically significant for 3 herbaceous pollens (*Artemisia*, Plantaginaceae and Poaceae) and 5 tree pollens (*Quercus*, Cupressaceae, *Fraxinus*, *Olea* and *Pinus*).

The relationship between pollen concentration and number of ARC cases changed depending on the age group and type of pollen. For people under 45 years, the risk of ARC associated with an interquartile increase in pollen concentration was significantly increased for all pollens studied, some with RR higher than others. In counterpart, for people from 45 to 64 years, the relationship was not significant for *Artemisia*, *Fraxinus* and *Pinus*. For people aged 65 and older, the risk remained significant only for Plantaginaceae, Poaceae and *Quercus* (Table 3).

The distribution of the risk over time (Fig. 2) showed that for Plantaginaceae, Poaceae and *Quercus* the risk of ARC cases associated with an interquartile increase in pollen concentration remained significant several days after the exposure, whereas for *Artemisia* and *Olea*, the risk is maximal on the day of the

Table 1 Total amount of pollen grains per cubic metre during the main pollen season in Montpellier and Nîmes 2004–2007

	2004		2005		2006		2007		Total	
	Montpellier	Nîmes	Montpellier	Nîmes	Montpellier	Nîmes	Montpellier	Nîmes	Montpellier	Nîmes
Ambrosia	155	151	72	123	130	234	127	160	484	668
Artemisia	118	102	129	98	107	80	129	72	483	352
Chenopodiaceae	317	229	342	216	313	231	419	233	1,391	909
Plantaginaceae	833	224	737	255	332	180	858	461	2,760	1,120
Poaceae	3,905	2,065	2,688	1,198	2,243	1,403	2,558	1,314	11,394	5,980
Urticaceae	3,924	2,107	3,092	1,861	1,567	1,159	2,161	1,497	10,744	6,624
Castaneae	2,709	1,973	1,720	1,047	1,008	591	894	1,076	6,331	4,687
Quercus	10,741	11,831	7,158	9,637	5,098	10,759	10,413	15,927	33,410	48,154
Cupressaceae	27,808	11,460	40,194	25,983	33,238	15,201	36,018	12,679	137,258	65,323
Fraxinus	5,855	929	5,548	549	7,432	1,428	4,193	764	23,028	3,670
Olea	722	1,014	981	725	769	1,107	521	594	2,993	3,440
Pinus	7,539	3,345	8,090	2,528	5,615	5,733	5,291	6,169	26,535	17,775
Populus	2,456	705	1,559	403	1,272	682	1,226	636	6,513	2,426
Platanus	5,078	660	4,413	423	4,958	1,093	5,610	1,160	20,059	3,336

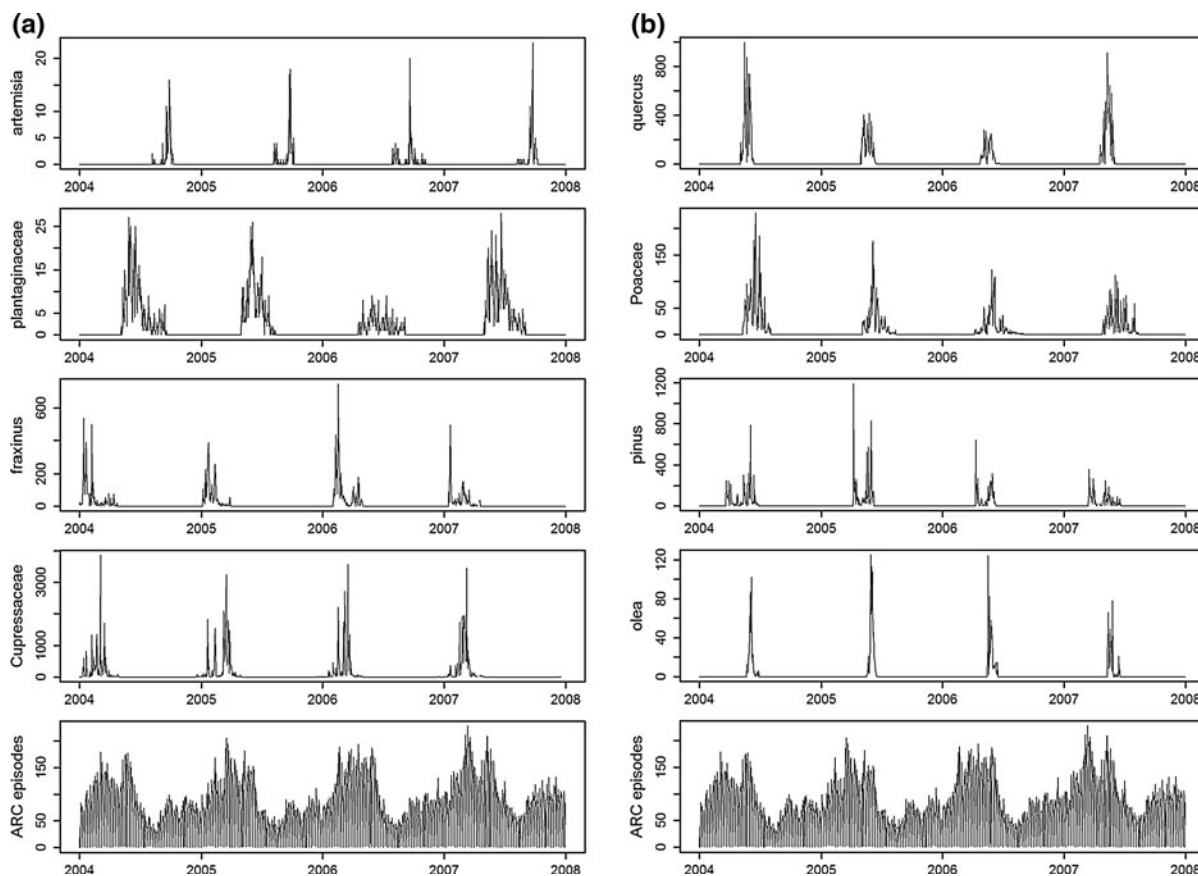


Fig. 1 **a** Daily number of treated allergic rhinitis and conjunctivitis (ARC) cases and daily pollen concentrations of *Artemisia*, *Plantaginaceae*, *Fraxinus* and *Cupressaceae* (measured in grains per cubic metre of air), Montpellier, France 2004–2007. **b** Daily

number of treated allergic rhinitis and conjunctivitis (ARC) cases and daily pollen concentrations of *Quercus*, *Poaceae*, *Pinus* and *Olea* (measured in grains per cubic metre of air), Montpellier, France 2004–2007

exposure. For *Cupressaceae*, the risk is significant the 5 days following the exposure but not the day of the exposure.

3.3 Urban area of Nîmes

From 2004 to 2007, the total number of ARC cases was estimated to be 78,072. Forty-one percentage occurred among persons aged 15–44 years, 27 % among people from 45 to 64 years, 15 % among children from 5 to 14 and 17 % among the 65 and older. Over the 4 years of the study, an average of 53 cases of ARC was recorded each day. The medians (ranges) of the minimum daily temperature, maximum daily temperature and the minimum daily relative humidity were, respectively, 10 °C (–6–24 °C), 21 °C (2–38 °C) and 39 % (9–97 %).

Table 4 shows the RR of ARC for a 2-day exposure and for a 6-day cumulative exposure associated with an interquartile increase in pollen concentration. The positive change in the risk of ARC, associated with a variation equal to an interquartile range of pollen distribution, was statistically significant for 2 herbaceous pollens (*Plantaginaceae* and *Poaceae*) and 4 tree pollens (*Quercus*, *Cupressaceae*, *Olea* and *Populus*). Looking at persons over 65 years old, the relation remained significant only for *Poaceae* and *Cupressaceae* (Table 5).

The distribution of the risk over time (Fig. 3) showed that for *Poaceae*, the risk of ARC cases associated with an interquartile increase in pollen concentration remained significant several days after the exposure, whereas for *Populus* and *Olea*, the risk is maximal the present day of the exposure. For

Table 2 Relative risk (RR) and 95 % confidence interval (95 % CI) of ARC estimated for a single-pollen model associated with a variation equal to an interquartile range of pollen distribution, Montpellier 2004–2007

Pollen	Interquartile range ^a	2-day exposure			6-day cumulative exposure	
		Exposure range used for the RR calculation ^a	RR	95 % CI	RR	95 % CI
Ambrosia	5	All	0.99	0.96–1.02	0.98	0.93–1.03
Artemisia	3	0–10	1.09	1.05–1.13	1.08	1.05–1.11
Chenopodiaceae	3	All	1.01	0.99–1.03	1.02	0.99–1.05
Plantaginaceae	6	All	1.10	1.08–1.13	1.17	1.13–1.21
Poaceae	31	0–90	1.13	1.10–1.17	1.11	1.08–1.14
Urticaceae	21	All	0.97	0.96–0.99	0.96	0.94–0.98
Castaneae	38	All	1.00	0.98–1.02	1.01	0.98–1.04
Quercus	220	All	1.15	1.12–1.18	1.26	1.21–1.31
Cupressaceae	212	0–600	1.09	1.06–1.13	1.05	1.04–1.06
Fraxinus	60	All	1.02	1.01–1.03	1.04	1.02–1.06
Olea	28	0–45	1.16	1.09–1.22	1.10	1.07–1.14
Pinus	89	All	1.02	1.01–1.04	1.06	1.03–1.08
Populus	60	All	1.01	0.99–1.03	1.00	0.97–1.03
Platanus	205	All	0.98	0.95–1.00	0.97	0.93–1.00

^a Variation in interquartile range of pollen concentration (measured in grains per cubic metre) based on days with non-zero pollen counts during the pollination periods between 2004 and 2007

Table 3 Relative risk (RR) of ARC and 95 % confidence interval (95 % CI), by age group, estimated for a single-pollen model associated with a variation equal to an interquartile range of pollen distribution for a 2-day exposure, Montpellier 2004–2007

Pollen	Interquartile range ^a	Exposure range used for the RR calculation ^a	5–14 years old		15–44 years old		45–64 years old		Over 65 years old	
			RR	CI	RR	95 % CI	RR	95 % CI	RR	95 % CI
Artemisia	3	0–10	1.24	1.15–1.33	1.11	1.06–1.17	1.06	1.00–1.13	0.94	0.87–1.02
Plantaginaceae	6	All	1.16	1.10–1.21	1.13	1.10–1.16	1.10	1.07–1.14	1.06	1.02–1.10
Poaceae	31	0–90	1.20	1.13–1.28	1.18	1.17–1.22	1.13	1.08–1.18	1.07	1.02–1.12
Quercus	220	All	1.21	1.17–1.29	1.19	1.15–1.23	1.10	1.05–1.15	1.08	1.03–1.14
Cupressaceae	212	0–600	1.09	1.03–1.17	1.11	1.07–1.16	1.10	1.06–1.15	1.05	1.00–1.11
Fraxinus	60	All	1.05	1.03–1.08	1.02	1.01–1.04	1.01	0.99–1.03	1.00	0.98–1.02
Olea	28	0–45	1.20	1.06–1.36	1.24	1.16–1.33	1.18	1.08–1.29	1.04	0.93–1.16
Pinus	89	All	1.05	1.02–1.08	1.03	1.01–1.04	1.02	1.00–1.04	1.02	0.99–1.05

^a Variation in interquartile range of pollen concentration (measured in grains per cubic metre) based on days with non-zero pollen counts during the pollination periods between 2004 and 2007

Cupressaceae, the risk is significant the 4 days following the exposure but not the day of the exposure.

4 Discussion

This study showed a significant association between pollen concentration in the air and the increase in the

number of deliveries in pharmacy for ARC in both urban areas of Montpellier and Nîmes. This relation was statistically significant in at least one of the two studied cities for Artemisia, Plantaginaceae, Poaceae, Cupressaceae, Quercus, Fraxinus, Olea, Pinus and Populus, taking into account temperature and relative humidity.

The study of the short-term effect of pollen exposure on ARC in the two studied areas highlighted

Fig. 2 Distribution over time of the increase in the risk of ARC associated with an interquartile increase in pollen concentration (risks estimated with a polynomial distributed lag model), Montpellier 2004–2007

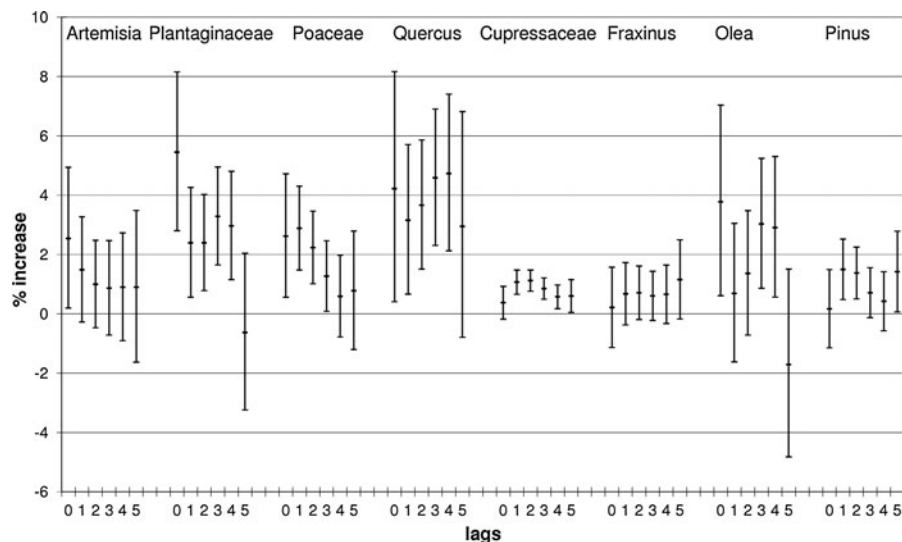


Table 4 Relative risk (RR) and 95 % confidence interval (95 % CI) of ARC estimated for a single-pollen model associated with a variation equal to an interquartile range of pollen distribution, Nîmes 2004–2007

Pollen	Interquartile range ^a	2-day exposure			6-day cumulative exposure	
		Exposure range used for the RR calculation	RR	(95 % CI)	RR	(95 % CI)
Ambrosia	5	Entire	1.00	0.97–1,02	1.03	0.99–1.07
Artemisia	2	Entire	1.01	0.97–1,04	1.02	0.97–1.08
Chenopodiaceae	2	Entire	1.00	0.97–1,02	1.01	0.97–1.04
Plantaginaceae	2	Entire	1.02	1.01–1,04	1.07	1.04–1.10
Poaceae	14	0–40	1.12	1.08–1,15	1.11	1.07–1.14
Urticaceae	13	Entire	0.97	0.95–0,99	0.93	0.91–0.96
Castaneae	40	Entire	0.99	0.96–1,02	1.00	0.96–1.04
Quercus	346	Entire	1.07	1.04–1,10	1.14	1.10–1.18
Cupressaceae	75	0–600	1.03	1.01–1,04	1.03	1.02–1.03
Fraxinus	9	Entire	1.00	0.98–1,01	1.01	0.99–1.03
Olea	30	0–60	1.15	1.09–1,21	1.08	1.05–1.12
Pinus	57	Entire	1.00	0.99–1,01	1.01	1.00–1.03
Populus	14	0–60	1.08	1.05–1,11	1.08	1.05–1.11
Platanus	30	Entire	0.98	0.95–1,00	0.96	0.92–0.99

^a Variation in interquartile range of pollen concentration (measured in grains per cubic metre) based on days with non-zero pollen counts during the pollination periods between 2004 and 2007

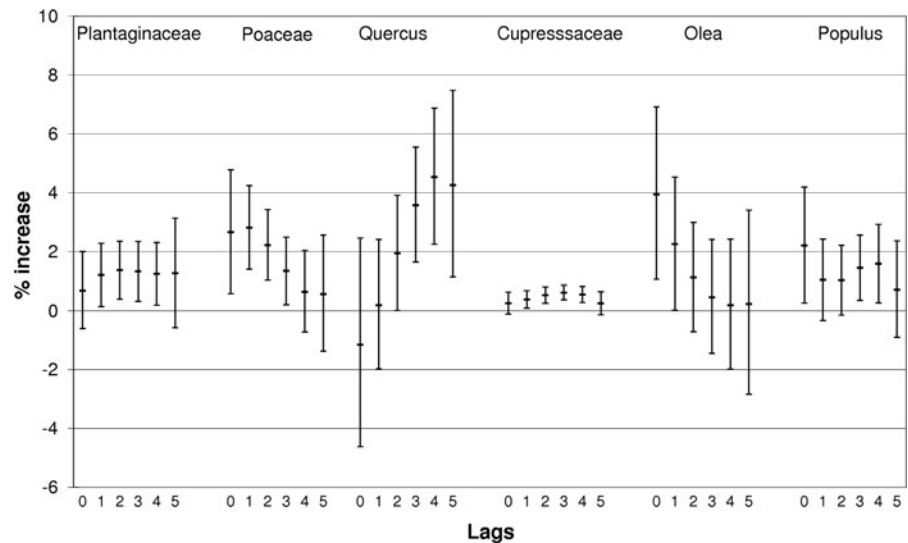
similar significant positive associations for the most allergenic pollens: Plantaginaceae, Poaceae, Quercus, Cupressaceae and Olea. In each city, for the majority of pollens studied, the risk of treated ARC cases decreased according to age and it was not significant beyond 65 years. These results are consistent with the literature (Bousquet et al. 2001; Schwartz 2000).

Cross-sectional surveys have shown that the prevalence of sensitization is lower in older adults, longitudinal surveys argued for a birth cohort effect (Jarvis et al. 2005). Another explanation is that diagnosis of allergic rhinitis in the elderly is more difficult because of other existing diseases that can produce similar symptoms. At last, treatment for allergic rhinitis is

Table 5 Relative risk (RR) of ARC and 95 % confidence interval (95 % CI), by age class, estimated for a single-pollen model associated with a variation equal to an interquartile range of pollen distribution for a 2-day exposure, Nîmes 2004–2007

Pollen	Interquartile range ^a	Exposure range used for the RR calculation	5–14 years old		15–44 years old		45–64 years old		Over 65 years old	
			RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI
Plantaginaceae	2	Entire	1.06	1.03–1.10	1.02	0.99–1.04	1.02	1.00–1.04	1.03	1.00–1.06
Poaceae	14	0–40	1.15	1.07–1.23	1.17	1.12–1.22	1.06	1.02–1.11	1.06	1.01–1.11
Quercus	346	Entire	1.13	1.07–1.19	1.08	1.04–1.12	1.04	1.00–1.08	1.04	0.98–1.11
Cupressaceae	75	0–600	1.03	1.00–1.06	1.03	1.01–1.05	1.04	1.03–1.06	1.05	1.03–1.06
Olea	30	0–60	1.27	1.14–1.41	1.21	1.12–1.29	1.10	1.03–1.19	1.05	0.93–1.19
Populus	14	0–60	1.06	1.00–1.13	1.06	1.03–1.09	1.10	1.06–1.15	1.05	0.98–1.12

^a Variation in interquartile range of pollen concentration (measured in grains per cubic metre) based on days with non-zero pollen counts during the pollination periods between 2004 and 2007

Fig. 3 Distribution over time of the increase in the risk of ARC associated with an interquartile increase in pollen concentration (risks estimated with a polynomial distributed lag model), Nîmes 2004–2007

complicated in older people by potential drug interactions (Busse and Kilaru 2009).

To our knowledge, very few studies analysed the short-term effect of pollen exposure on the number of ARC. A Canadian study showed a significant relationship between overconsultation for allergic rhinitis and Ambrosia pollen concentration (Breton et al. 2006). In a study similar to ours, realized in Clermont-Ferrand (Zeghnoun et al. 2005), the same association was observed between Poaceae, Fraxinus and Quercus pollen and the number of ARC treated. The Clermont-Ferrand study underlined a relationship for Betula and Corylus pollens as well. Those two pollens are specific of tempered area and are weakly represented in the atmosphere of Nîmes and Montpellier.

Many studies demonstrated a significant correlation between pollen concentration and several respiratory pathologies. An Australian study (Hanigan and Johnston 2007) underlined an association between respiratory hospital admissions, daily total pollen counts and Myrticaceae pollens concentration. A significant correlation was found between daily pollen counts and emergency admissions for asthma attack in several studies in Spain (Tobias et al. 2003, 2004) and Canada (Dales et al. 2004; Stieb et al. 2000).

Artemisia, Poaceae, Plantaginaceae, Cupressaceae, Olea and pollens are known as allergenic pollens (D'Amato et al. 2007), and they were found significantly associated to the number of ARC cases in our study. The allergenicity of Populus, Fraxinus and

Quercus is not well illustrated in the literature, but an association was found in our study between the number of ARC and pollen levels in the air. The fact that RRs were alike for Poaceae and *Quercus* might be due to overlapping in pollination periods of these two pollens. In the same way, the association between ARC episodes and *Populus* in Nîmes and the association between *Fraxinus* and ARC episode in Montpellier may partly be explained by overlapping in main pollen seasons with Cupressaceae. In our study, *Ambrosia* pollens, despite their allergenic character, were not found associated with ARC. This result was expected because, contrary to other areas in France (Thibaudon et al. 2004) or countries in the world (Breton et al. 2006; Stefanic et al. 2005), *Ambrosia* has not colonized the areas of Nîmes and Montpellier yet: the pollen grains of *Ambrosia* measured in Montpellier and in Nîmes were carried by the wind from northern areas (Agence Méditerranéenne de l'Environnement 2005).

The studied population is urban. Because the risk of allergy and exposure to pollen is likely to be different in a rural area, our results cannot be extrapolated in the countryside, and thus, it would be interesting to carry out the same type of study in a rural area. However, such a study would require implanting pollen captors in the countryside.

In our study, an ARC case was defined as the association of an oral antihistamine and of a local antiallergic drug on the same medical prescription. This definition could be restrictive because only an antihistamine or a local antiallergic drug can be used to treat ARC. This restriction guarantees a good, but not perfect, specificity to our health indicator because antihistamine and nasal corticoids are sometimes used to treat non-allergic rhinitis or perennial rhinitis caused by mites, cats, etc. Our health indicator does not include patients buying drugs without medical prescription or patients who do not suffer from an ARC severe enough for consulting a doctor. Because a delay between the first symptoms and the purchase of the drugs in pharmacy may exist, our health indicator would be rather representative of symptoms occurred a few days before the purchase. Nevertheless, ARC symptoms being severe, it can be assumed that this delay is fairly short.

Compared to other species and taking into account the allergenic nature of Poaceae pollens, the RR estimated for this pollen is quite low (RR: 1.13; 95 %

confidence interval (CI) 1.10–1.17 in Montpellier for a 2-day exposure). As Grass pollen (Poaceae) is the major cause of pollinosis in the world, this result could be explained by preventive purchases more developed by people suffering from this allergy. Thus, the RR for Poaceae pollen might be underestimated in our study.

RR estimated for an exposure to Cupressaceae, although significant in the two studied areas, was relatively low (1.09 in Montpellier and 1.03 in Nîmes) given the high concentrations recorded. However, as for Poaceae, the role of Cupressaceae in inducing ARC has already been described and its pollination period, although varying every year in terms of duration and intensity pollination, is well known (Bousquet et al. 2001; Charpin et al. 2005). So it is possible that treatments are often prescribed before the pollination period. Moreover, the pollination period for Cupressaceae occurs in winter, and misdiagnosis with infectious rhinitis is possible at this time of year.

The method used to measure pollen concentrations (Hirst trap) guarantees data of a good quality. However, the exposure indicator expresses an average exposure of the population but does not represent an individual exposure. Because the number of grains must be different according to the location of the captor in the city and thus its proximity to some species, the data regarding pollen concentration have to be considered as increases and decreases and not as absolute values. And so the quantification of the RR by an interquartile increase seems to be relevant.

The short-term effect of pollen exposure on ARC was estimated using a GAM. When the relationship between number of pollen grains in the air and ARC was not linear and presented a slowdown point, the risk was calculated only for an exposure range from 0 grains of pollen to the slowdown point. In this hypothesis, the RR might be overestimated. In counterpart, using a generalized additive distributed lag model might underestimate the RR in case of a non-linear relationship between the increase in pollen concentration and the increased in RCA cases. Single-pollen models were used, but the risk associated with each individual species is difficult to ascertain because several species pollinate at the same time. This overlapping can lead to show significant associations for non-allergenic pollen: the significant risk observed for *Pinus* in Montpellier could be explained by its pollination period concomitant with *Olea*, Poaceae and Urticaceae.

As a conclusion, this study showed an association between ARC cases and two typical Mediterranean pollens: Cupressaceae and Olea. Initiatives should be taken to reduce Cupressaceae planting and to develop diversified alternative lines instead. Individual should be warned about the allergenic potential of Olea pollen because of its increasing implantation in gardens.

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