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C Ravault, A Zegnhoun, B Fabres, J Lecadet, P. Quenel, et al.. Short-term effects of airborne pollen content on the risk of allergic rhinoconjunctivitis in Clermont-Ferrand, France, 2000-2001. Archives of Environmental & Occupational Health, 2005, 60 (3), pp.170-176. hal-04825656

HAL Id: hal-04825656 https://hal.science/hal-04825656v1

Submitted on 13 Dec 2024

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Short-term effects of airborne pollen content on the risk of allergic rhinoconjunctivitis in Clermont-Ferrand, France, 2000-2001.

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Abstract

Allergies caused by pollens affect 10 to 15% of the general population. A pilot study was carried out in Clermont-Ferrand (France) over 2000-2001 to analyse the short-term relationship between the daily variations in rhinitis and/or allergic conjunctivitis and the daily variation in pollen counts in the ambient air.

ERASME data (French National Health datawarehouse) made it possible to identify all the subjects to whom at least one drug was prescribed to treat a rhinitis or an allergic conjunctivitis. One case of allergic rhino-conjunctivitis (ARC) was defined according to the following criteria: i) was domiciled in the study area, ii) was 5 years old or over and iii) had on a given day, a prescription for an oral antihistamine associated with a local treatment for allergic rhinitis, for allergic conjunctivitis, or for both. Ten allergenic pollens and a pollen control were studied. A Poisson regression model using penalized Spline functions was used.

A positive and significant association was found for pollens of Betula, Cupressaceae, Quercus, Fraxinus and Poaceae. The relative risks varied between 1.3 (IC95 % :1.0-1.5) and 1.2 (IC95 % :1.1-1.5) for an interquartile range increase of daily pollen counts of Cupressaceae (13 grains/m3) and of Betula (45 grains/m3) respectively.

Further analyses are necessary to confirm these results, in particular using longer time series of pollen and drug prescription.

Subtitle: Airborne pollen content and risk of allergic rhino-conjunctivitis

Key words:

Pollen, Allergic rhino-conjunctivitis, Air pollution, Anti-allergic drug prescription.

Introduction

Allergies caused by pollen cover clinical manifestations due to allergy to pollens. Most often allergic rhinitis or "hay fever" is frequently associated with an allergic conjunctivitis. It is also often associated with asthma, and it can have complications with local infections (sinusitis in particular). The pollen rhinitis affects 10 to 20 % of the general population in Europe [1]. In France, 18.5 % of adults from 20 to 60 years old are affected [2] and in 13–14-year-old teenagers, the prevalence varies between 11 and 27 % according to study region [3]. As all allergic diseases, pollen rhinitis has constantly increased for several ten years, in particular in urban areas [4]. In addition, the allergic rhinitis represents a significant socio-economical cost and generates an alteration of the quality of life [1,5]. Finally, it can be associated with asthma of which the evolution can be serious.

Very often, studies on the subject are clinical and targeted at defining "clinical" thresholds, that is to say thresholds for which the pollen causes clinical manifestations in a sensitised subject or worsen a pre-existing symptomatology [4, 6-7]. These studies are only based on specific populations (subjects allergic to one or several allergenic pollens) and thus they cannot answer the question about the exposure-risk relationship in the general population.

Time series-type studies are not numerous [8-14] and only one study carried out in Canada, aimed at studying the pollens- allergic rhino-conjunctivitis (ARC) relationship [10]. In France, to our knowledge, there are no time series-type studies aimed at characterizing the relationship between the exposure to allergenic pollens and the risk of pollinosis in the general population [x]. QUENEL P., CHAMBAUD L., LE GOASTER C., THIBAUDON M., ALMOUSSA M., LAFOREST L. Associations entre les concentrations aériennes de pollens et les pollinoses saisonnières : synthèse des études épidémiologiques publiées entre 1978 et 1995. *Revue d'épidémiologie et de Santé Publique 1997;45:224-236*

This work aims at studying the daily variations of pollen levels in relation with the incidence of ARCs in the general population using a health indicator based on drugs prescribed and delivered by chemists and an indicator of exposure to pollens.

Materials and Methods

The study area encompasses the city of Clermont-Ferrand and 17 villages located at a maximum distance of 13 Km from Clermont-Ferrand, being a population of around 261 000 inhabitants. The study period covers two pollen seasons, 2000 and 2001.

Health data

Drug data is from the Erasme database and is provided by the French Health Insurance of Clermont-Ferrand agglomeration. The studied population consists of contributors affiliated to general regime of social security and domiciled in Clermont-Ferrand agglomeration in 2000 and 2001 as well as their beneficiaries. The general regime covers 69 % of the population of Puy-de-Dôme department with a rate over 80 % in the urban area. Data from Erasme database made it possible to identify all subjects with a prescription for at least one drug appearing on a pre-established list (table 1), prescribed and reimbursed by the social security, over 2000 and 2001 and within the studied area. The target drugs were oral antihistamine and local forms for the treatment of ARCs (antihistamine, steroid anti-inflammatory, anti-cholinergic and anti-allergic non antihistaminic product based nasal preparations, antihistamine or non-antihistamine based local anti-allergic eye drops).

The decision was made to build a very specific indicator for this pathology to study the relationship between the airborne pollen concentration and the risk of ARC. A case of ARC was defined according to the following age and treatment criteria: i) the identified subjects should be over 5 years old, the diagnostic of pollinosis being rare and difficult to establish under this age; ii) a case was a subject who, on a given day, had a prescription to obtain at chemist's a treatment by oral antihistamine associated with a local treatment for an allergic rhinitis or a treatment for an allergic conjunctivitis, or for both. The health indicator was built aggregating each day the number of ARC cases in the studied population as a whole (5 years old or over) and by age class (5-14 years old, 15-44 years old, 45-64 years old and 65 years old and over).

Exposure data

Exposure data to pollens was provided by the French Aerobiology Network (Réseau national de surveillance aérobiologique - RNSA) which manages a network of 50 pollen measurement stations installed through out France. The measurement stations use the volumetric technique, enabling a daily counting of the different pollens collected [15]. In Clermont-Ferrand, the RNSA has one measurement station located on the roof of the Montpied Hospital, at a height of 30 m.

Eleven allergenic pollens significantly involved in respiratory allergies in Clermont-Ferrand (eight pollens from trees and three from herbaceous plants) as well as a non-allergenic pollen, the Pinus pollen, taken as a control pollen have been studied. All these pollens come from strictly anemophilous plants except the Salix which is anemophilous and entomophilous. Their diameter is more often between 20 and 30 µm. The exposure indicator corresponds to the number of grains per cube metre of air sampled every day in Clermont-Ferrand for each of the 12 studied pollens. This exposure indicator is aggregated and reflects the daily exposure to the ambient air pollen concentration of the entire population from the Clermont-Ferrand agglomeration.

Cofactors

Air pollution data was provided by the urban station of the Clermont-Ferrand city centre. For 2000 and 2001, the following pollutants are available: ozone, black smokes, sulphur dioxide, carbon monoxide, suspended particles, nitrogen dioxide and nitrogen monoxide.

The following meteorological data was provided by the Météo-France station of Aulnat located at 5 km to the East of Clermont-Ferrand: daily minimum temperature, daily maximum temperature, daily minimum relative humidity, daily maximum relative humidity, quantity of precipitations in millimetres per day.

Statistical analysis

The short-term relationship between the daily number of pollen grains in ambient air and the daily number of ARC cases was studied using a Poisson Regression Model [16-17] with penalized *spline* functions [18-19] which made it possible to take into account possible non linear effects of the variables included in the model.. This model enabled, on the one hand to control the over-dispersion of health data and, on the other hand, to control the seasonal variations, the meteorological and air pollution variables. Binary variables have also been used for the week days, holiday days and school holidays.

Different lags between the exposure to meteorological, air pollution and pollen indicators and the appearance of ARC cases were tested (lags from 0 to 3 days and cumulated effect of several days of exposure). The choice between these different lags as well as the different meteorological and air pollution variables was based on the Akaike criterion [20]. At the end, the model consists of the following variables: trend and seasonal variations, days of the week, holiday days, school holidays, maximum temperature, minimum relative humidity, mean precipitations and ozone.

The residuals analysis (partial autocorrelation functions) enabled checking the lack of fit of the model and the possible presence of residual autocorrelations. The analysis was carried out using the R software [21].

RESULTS

Health indicator

The temporal evolution of the number of ARC cases is represented graphically in figure 1. Over the entire study period, on average, 26 ARC cases have been observed per day (table 2). This number varied between 3 (5-14 years old) and 12 (15-44 years old) cases per day according to the age classes.

Pollen exposure indicator

In figure 1 the periods of pollination between 2000 and 2001 in Clermont-Ferrand are presented. The mean concentration of pollen grains varied from one pollen to another (table 2) with a daily average of at least 5 grains per cube metre for the Plantaginaceae, the Platanus and the Salix and at the most 61 grains per cube metre of air for the Poaceae.

Factors of confusion

Regarding the meteorological factors, the maximum mean temperature was 17° C, the minimum relative humidity was 49 % on average and the mean precipitations were 15 mm over the 2000-200 period (table 3). For the air pollution indicators, the daily mean concentrations varied between 4 µg/m3 for sulphur dioxide and 50 µg/m3 for ozone. The ozone levels are higher between April and September, that is to say more than half of the pollen season.

Short-term effect of airborne pollen concentration on the risk of ARC

The short-term association between exposure to pollens and the risk of ARC is presented in tables 4 and 5 by relative risk (RR) for an interquartile increase of pollen levels. The lags observed between pollen exposure and the ARCs varied more often between 0 and 3 days.

Over the whole studied population, the RR were over 1 for all pollens except for Alnus and Pinus pollens. The association was statistically significant for the Poaceae, the Quercus, the Betula, the Fraxinus and the Cupressaceae: the relative risk varied between 1.03 (Cupressaceae) and 1.22 (Betula and Fraxinus).

For subjects aged 5-14 years old, the RR of ARC was over 1 for all the pollens from allergenic trees (Betula, Cupressaceae, Quercus, Platanus, Fraxinus, Salix, Alnus, Corylus) and varied between 1.01 (Corylus) and 1.30 (Fraxinus) (table 4). However, it was only statistically significant for the Betula, the Quercus and the Fraxinus. For herbaceous plants, the RR varied between 1.08 (Artemisia) and 1.23 (Plantaginaceae) and was only statistically significant for the Poaceae and the Plantaginaceae.

For subjects aged 15-44 years old, the RR was positive for all the pollens from allergenic trees, except for the Alnus, and varied between 1.03 (Cupressaceae and Corylus) and 1.40 (Fraxinus). It was statistically significant for the Betula, the Cupressaceae, the Quercus, the Fraxinus and the Salix. For herbaceous plants, the RR was only positive for the Poaceae and the Artemisia but remains statistically non significant.

For subjects aged 45-64 years old, the RR was positive for all the pollens from allergenic trees except for the Corylus and varied between 1.03 (Cupressaceae) and 1.27 (Platanus). It was statistically

significant for all except for the Alnus. For the herbaceous plants, the RR was positive but statistically non significant.

Regarding subjects aged 65 yeas and more, the RR was positive for all the pollens from allergenic trees, varied between 1.01 (Platanus) and 1.14 (Alnus). It was statistically significant for the Betula, the Cupressaceae, the Quercus, the Alnus and the Corylus. For the herbaceous plants, the RR was only positive and statistically significant for the Poaceae (1.09) and the Plantaginaceae (1.13).

Regarding Pinus, the RR varied between 0.98 (45-64 years old) and 1.02 (5-14 years old and over 65 years old) but were never statistically significant.

DISCUSSION

This pilot study enabled quantifying the exposure-risk relationship for 11 pollens. The associations were, generally, positive for all the studied allergenic pollens. Nevertheless, they were only significant for the Quercus, the Betula, the Fraxinus and the Cupressaceae, and to a lesser extent, for the Poaceae.

For the pollens of Quercus, Betula, Fraxinus, Cupressaceae and Poaceae, the distribution of RR per age class shows three different profiles:

- For an exposure to pollens of Quercus, of Betula and of Fraxinus, the risk of ARC was maximum for the age class of 15-44 years old, with RR over 1.30 for an increase of the air concentration of pollens varying between 28 (Fraxinus) and 45 (Betula) grains per m³;
- For an exposure to pollens of Cupressaceae, the RR of ARC increased with the age classes to reach its maximum for the oldest subjects (RR=1.10 for an increase of the pollen concentration of 13 grains per m³);
- For an exposure to pollens of Poaceae, the RR was higher in young subjects (5-14 years old) and in the oldest (65 years old and over), with a RR about 1.10 for an increase of 55 grains per m³ of the pollen concentration.

In national and international literature, there are few results about the relationship between exposure to pollens and the risk of ARC in the general population. Thus, six studies have studied the short-term pollens-health relationship using the analysis of time series [8-14]. Only one study is concerned in the risk of ARC [10], the authors showing an increase in the risk of emergency hospital admissions for rhinitis and allergic conjunctivitis related to an increase of pollen exposure. The other five studies concerned other pathologies: cardiovascular diseases [9], asthma [8, 11-14].

In this study, the method of construction of the ARC indicator was based on very strict criteria: exclusion of children under five years old in whom the diagnostic of pollinosis is not very frequent and not very reliable; definition of a case based on an association of drugs, prescribed specifically for a

rhinitis and/or an allergic conjunctivitis, and delivered on a given day at a chemist's. This method has the advantage of targeting individuals really suffering ARC. The disadvantage is to reduce the daily number of ARC cases and thus to reduce the power of the study. The estimated prevalence of treated ARC was 2.5 % with the health indicator of the study for a prevalence of the symptoms for seasonal rhinitis (principally pollen) estimated between 11 and 27 % in the general population according to the studied French regions [2-3]. Sensitivity analyses would be interesting to perform in order to more precisely define the relevant drug associations and thus to increase the power of the study. However, the specificity of this indicator was not perfect, the used drug associations could be prescribed for non-allergenic rhinitis, or to correspond to renewals of treatment and not to acute episodes.

The use of drug data provided by Health insurance only identifies the subjects who consult the physician for their pathology and who buy their drugs. The individuals for whom the discomfort is not sufficient to induce a resort to cares are not identified, as well as allergic persons who have antiallergic drugs and use them by self-medication.

Regarding classification errors, a first type of error concerns the classification in status ill/non-ill. Actually, at the beginning of the pollen season, season which can occur really early, in January-February, for some trees, the diagnostic of pollen allergy is not evident. Besides Lecadet and coll [22] showed a peak of antibiotic prescriptions at the beginning of the year in Clermont-Ferrand, which can be explained in part by the diagnostic of infectious rather than pollen rhinitis. This could be an explanation for the absence of observed relationship for the Alnus pollens.

A second type of error can occur for the date of appearance of symptoms. Actually, in the analysis, the date of appearance of the symptoms was considered as that of drug delivery, available in the database. No check can be made on this point. However, Lecadet and coll [22] showed that at the time of summer period, the consumption of anti-allergic drugs was low, compensated by a consumption renewal either before or after the holidays. This observation is in favour of the hypothesis that patients take precautions and buy their treatment in a preventive way, thus before the appearance of the symptoms. This can be an explanation to the low relationship observed for all Poaceae in particular. Actually, this preventive attitude is certainly highly developed for a seasonal classic allergy as the allergy to Poaceae ("hay fever") than for less known allergies to some tree pollens, which can explain the low relationship observed for the Poaceae but a positive and significant relationship for several tree pollens.

Regarding the exposure indicator, the pollen mean concentration over 24 hours was taken into account. Thanks to the method of pollen capture used by the RNSA, it is possible to calculate the diurnal pollen concentration, more relevant for use as exposure indicator because the plants do not pollinate during the night and the people are not exposed to it. The indicator of exposure characterizes in a global way the exposure of the population and does not indicate a direct individual exposure.

However, some pollens scatter at a short distance regarding their place of emission (Platanus, Salix), and thus will only cause symptoms in case of proximity exposure.

Although all the studied pollens are highly allergenic, positive and significant associations was only observed constantly into the different age classes for the pollens of Betula, Quercus, Fraxinus and Cupressaceae, and to a lesser extent, for the pollens of Poaceae. Among the studied plants, it deals with the plants which pollinate more in the Clermont-Ferrand region. For the other pollens, the absence of constant relationship can be explained by short and reduced pollination period. Actually, the Artemisia, the Plantaginaceae, the Platanus and the Salix are plants which did not pollinate to a great extent over the study period. In addition, the study only lasts two years which can reduce the statistical power.

The results observed in the study are really encouraging for the continuation of this work. Additional analyses over a longer period are still necessary to confirm these results.

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Table 1.List of targeted antiallergic drugs according to the International Nonproprietary
Name (INN) and the French speciality name

General antiallergic drugs: Antihistamines H1

loratadine (Clarityne [®]) astemizole (Hismanal [®]) fexofenadine (Telfast [®] 120 mg) cetirizine (Virlix® - Zyrtec [®] 10 mg) carbinoxamine (Allergefon [®])	brompheniramine (Dimégan [®]) doxylamine (Méréprine [®]) cyproheptadine (Périactine [®]) promethazine (Phénergan [®]) dexchlorpheniramine (Polaramine [®])
buclizine (Aphilan®)	mequitazine (Primalan®)

Local forms for allergic rhinitis

 beclometasone (Béclo-rhino® - Béconase® - Rhinirex[®]) fluticasone (Flixonase[®]) triamcinolone (Nasacort[®]) flunisolide (Nasalide[®]) tixocortol neomycine (Pivalone®) 	prednisolone (Solucort [®]) azelastine (Allergodil [®]) ipratropium bromide (Atrovent [®]) sodium cromoglycate (Lomusol [®]) N-acetyl-aspartyl-glutamic acid (Rhinaaxia [®])
Local antialle	rgic eye drops
sodium cromoglycate (Cromabak [®] - Cromedil [®] - Cromoptic [®] - Opticron [®]) N-acetyl-aspartyl-glutamic acid (Naabak [®] - Naaxia [®])	levocabastine (Lévophta [®]) lodoxamide (Almide [®]) nedocromil (Tilavist [®])

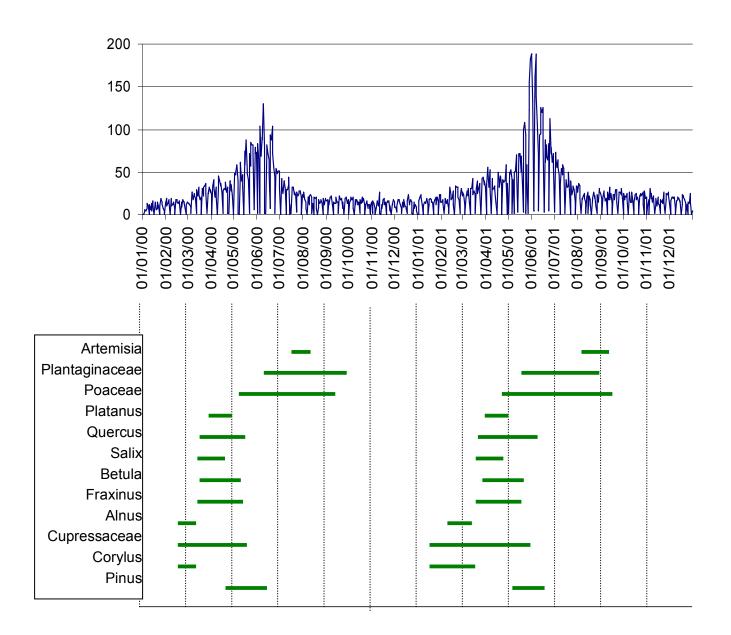


Figure 1. Daily number of Arc cases (all ages), and pollination periods, Clermont-Ferrand, 2000-2001

ARC		Average (standard deviation)	1 st quartile	2 nd quartile	3 rd quartile	Max
All ages		26 (27.0)	11	19	31	189
5-14		3 (5.5)	0	1	4	57
15-44		12 (14.9)	3	7	13	123
45-64		7 (5.8)	3	6	10	36
\ge 65 years		4 (3.2)	1	3	6	20
Pollen	Pollination period (days)					
Artemisia	68	7 (7.6)	2	4	9	28
Plantaginaceae	219	5 (4.1)	2	4	7	21
Poaceae	282	61 (107.8)) 4	12	59	662
Platanus	67	5 (6.2)	1	2	6	31
Quercus	125	37 (71.4)	2	8	37	437
Salix	107	5 (4.8)	2	3	6	25
Betula	132	35 (50.2)	2	12	47	284
Fraxinus	126	27 (36.1)	4	12	32	187
Alnus	84	20 (33.0)	2	8	21	179
Cupressaceae	270	16 (30.2)	2	4	15	277
Corylus	95	21 (35.9)	2	8	17	222
Pinus	201	25 (66.4)	1	3	14	558

Table 2.Distribution of daily number of ARC cases per age classes and of daily number ofpollen grains per m³ over the pollen season of each pollen, Clermont-Ferrand, 2000-2001

	Average (standard deviation)	Min	1 st Quartile	Median	3 rd Quartile	Max
Maximum temperature (°C)	17 (8.0)	-5	12	17	23	36
Minimum humidity (%)	49 (14.1)	11	40	49	57	93
Precipitation (mm)	15 (47.7)	0	0	0,1	6	514
Sulphur Dioxide (µg/m³)	4 (4.4)	0	2	3	6	30
Particles (µg/m ³)	19,0 (8.1)	5	13	17	23	59
Black smokes (µg/m ³)	10 (10.2)	0	4	6	11	79
Nitrogen dioxide (µg/m ³)	31 (14.7)	4	21	29	39	96
Ozone (µg/m ³)	50 (22.4)	3	34	51	66	114

Table 3.Daily distribution of meteorological and atmospheric pollution variables in Clermont-
Ferrand, 2000-2001

Table 4- Relative risks of ARC (all ages) estimated for an interquartile increase of the numberof pollen grains, Clermont-Ferrand, 2000-2001

			All ages
	Interquartile Interval	Delay	RR IC95%
Artemisia	7	0-1d	1.02 [0.95-1.09]
Plantaginaceae	5	0d	1.01 [0.97-1.05]
Poaceae	55	0-1d	1.04 [1.00-1.08] ^a
Platanus	5	0-1d	1.05 [0.96-1.16]
Quercus	35	0-1d	1.11 [1.05-1.16] ^a
Salix	4	0-1d	1.03 [0.99-1.07]
Betula	45	0-1d	1.22 [1.11-1.35]ª
Fraxinus	28	0-1d	1.22 [1.13-1.31] ^a
Alnus	19	0-1d	0.99 [0.96-1.02]
Cupressaceae	13	0-1d	1.03 [1.00-1.05] ^a
Corylus	15	0-1d	1.02 [0.99-1.06]
Pinus	13	0-1d	1.00 [0.99-1.02]

^a p<0.05

	Interquartile	5-14 years		15-44 years		45-64 years		\geq 65 years		
	interval	Delay	RR	IC95%	Delay	RRIC95%	Delay	RRIC95%	Delay	RRIC95%
Artemisia	7	0d	1.08	[0.91-1.29]	1d	1.05[0.94-1.16]	0d	1.08[0.97-1.21]	0-1d	0.96[0.83-1.11]
Plantaginace ae	5	2d	1.23	[1.09-1.38]	0-1d	0.96[0.89-1.03]	0d	1.07[0.98-1.16]	0d	1.13[1.02-1.24]
Poaceae	55	2-3d	1.11	[1.04-1.19]	1-2d	1.05[0.99-1.11]	0d	1.01[0.97-1.05]	0-1d	1.09[1.04-1.14]
Platanus	5	0d	1.03	[0.93-1.13]	0d	1.04[0.98-1.11]	0d	1.27[1.10-1.46]	1d	1.01[0.93-1.10]
Quercus	35	1-2d	1.20	[1.02-1.41]	1-2d	1.31[1.13-1.53]	0d	1.13[1.06-1.21]	0-1d	1.05[1.01-1.10]
Salix	4	2d	1.07	[0.96-1.19]	0-1d	1.07[1.01-1.13]	0-1d	1.07[1.01-1.13]	0-1d	1.05[0.97-1.14]
Betula	45	0d	1.23	[1.07-1.43]	0d	1.31[1.19-1.44]	2d	1.16[1.05-1.28]	1d	1.09[1.00-1.19]
Fraxinus	28	0-1d	1.30	[1.07-1.58]	0-1d	1.40[1.25-1.56]	0d	1.18[1.08-1.30]	0-1d	1.07[0.99-1.15]
Alnus	19	1d	1.12	[0.96-1.30]	0-1d	1.00[0.95-1.06]	0d	1.06[0.97-1.16]	0d	1.14[1.02-1.27]
Cupressace ae	13	0-1d	1.02	[0.96-1.09]	0d	1.03[1.01-1.05]	0-1d	1.03[1.00-1.07]	0-1d	1.10[1.02-1.18]
Corylus	15	0d	1.01	[0.94-1.10]	0-1d	1.03[0.97-1.09]	0-1d	1.00[0.97-1.04]	0-1d	1.08[1.00-1.15]
Pinus	13	0-1d	1.02	[0.99-1.05]	0-1d	1.00[0.98-1.03]	0-1d	0.98[0.95-1.01]	0-1d	1.02[0.99-1.06]

Table 5. Relative risks of ARC observed for an interquartile increase of the number of pollen grains per age classes

Model including: trend and seasonality, days of week, bank holiday days, school holidays, maximal temperature, minimum relative humidity, precipitations (daily average) and ozone (daily average) at delay 1 day. 0-1d = average of the exposure of the day and of the day before, 1-2d = average of the exposure of the day before and of the two-days before.