ORIGINAL ARTICLE

Short-term Effects of Airborne Ragweed Pollen on Clinical Symptoms of Hay fever in a Panel of 30 Patients

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Abstract

Objectives: Ragweed, *Ambrosia artemisiifolia*, is a highly allergenic annual herbaceous plant that is spreading quickly across the globe. Few studies have investigated the relationship between ragweed pollen counts and hay fever symptoms. We investigate the dose-response relationship between ragweed exposure in patients sensitized to ragweed and daily hay fever symptoms.
Method: A panel study was conducted among 31 adult patients sensitized to *A artemisiifolia* in France and Switzerland. Rhinitis, conjunctivitis, and bronchial symptoms were recorded daily, as well as daily pollen counts of ragweed, air pollutants, and meteorological data over 2 successive years. Data were analyzed with generalized estimating equation models to quantify effects of ragweed pollen whilst controlling for confounders.
Results: The relationship between ragweed pollen and the percentage of patients with nasal, ocular, and bronchial symptoms was linear. For every increase of 10 grains/m^3, the odds ratio (OR) (95% confidence interval) for nasal symptoms was, in 2009, 1.18 [1.04-1.35] on weekdays and 1.43 [1.16-1.75] at weekends, and in 2010, 1.04 [1.00-1.07] on weekdays and 1.25 [1.06-1.46] at weekends. The OR for ocular symptoms was 1.32 [1.16-1.56] in 2009 and 1.05 [1.02-1.07] in 2010. Finally, the OR for bronchial symptoms was 1.14 [1.03-1.25] in 2009 and 1.03 [0.97-1.08] in 2010.
Conclusion: There is a statistically significant linear relationship between ragweed pollen counts and hay fever symptoms. Our study shows that nasal symptoms differ on weekdays and at weekends.

Key words: Air pollution. Epidemiology. Hay fever. Meteorological factors. Panel study. Pollen. Ragweed.

Resumen

Objetivos: La Ambrosia *artemisiifolia* es una planta herbácea, altamente alergénica, que tiende a extenderse mundialmente muy rápidamente. Muy pocos estudios han investigado la relación de los contajes de polen de ambrosia con la intensidad de los síntomas. En este trabajo hemos documentado la relación dosis/respuesta entre la exposición a ambrosia, en pacientes sensibilizados a este polen, y la intensidad de su sintomatología
Métodos: En el estudio se incluyeron 31 pacientes residentes en Francia o Suiza y sensibilizados a Ambrosia *artemisiifolia*. Durante dos años consecutivos, se registraron diariamente los síntomas oculares, nasales y bronquiales de los pacientes, los niveles de polen de ambrosía, los niveles de contaminantes ambientales junto con los datos. El análisis de los datos se realizó mediante la construcción de modelos de ecuaciones de estimación generalizada, de forma que se pudiera cuantificar los efectos del polen de ambrosia y controlando las variables de confusión.
Resultados: La relación entre los recuentos de polen de ambrosía y el porcentaje de pacientes con síntomas nasales, oculares y bronquiales fue linear. Para cada incremento de 10 granos/m^3, el OR para los síntomas nasales, en el año 2009, fue 1.18 [1.04-1.35] durante los días entre semana, y 1.43 [1.16-1.75] durante el fin de semana, y en 2010, 1.04 [1.00-1.07] durante los días entre semana y 1.25 [1.06-1.46] durante el fin de semana; el OR para los síntomas oculares fue de 1.32 [1.16-1.56] en el 2009 y 1.05 [1.02-1.07] en el 2010; el OR para los síntomas bronquiales fue 1.14 [1.03-1.25] en 2009 y 1.03 [0.97-1.08] en 2010.
Conclusión: Hemos demostrado una relación lineal significativa entre los recuentos de polen de ambrosía y los síntomas de la polinosis en los pacientes sensibilizados. Nuestro estudio también demostró que el nivel de molestias difiere entre los días entre semana comparados con los del fin de semana.

Palabras clave: Contaminación ambiental. Epidemiología. Rinitis alérgica. Factores meteorológicos. Polen. Ambrosia.

Introduction

Short ragweed (*Ambrosia artemisiifolia*) is an annual herbaceous plant from the Asteraceae family. Ragweed is wind-pollinated and produces high quantities of pollen. *A artemisiifolia* spreads exceptionally quickly. A single plant can generate an average of 3000 to 6000 seeds and some specimens can produce as many as 60 000 [1]. Furthermore, it is now well documented that ragweed pollen can travel long distances [2]. Most European ragweed species are imported from North America, where they are native and widespread. In Europe, the countries with the highest concentrations of ragweed are Hungary, Italy, Croatia, and France (Rhône-Alpes region and Burgundy) [3]. Human activities, such as those related to traffic, agriculture, and birdseed, are the main cause of the introduction of ragweed to different European regions [4].

Prevalence of sensitization to ragweed in the general population differs between the United States and Western Europe. In the 2005-2006 US National Health and Nutrition Examination Survey (NHANES), the prevalence of specific IgE to ragweed was 15.6% [5], which is considerably higher than the rate of 0.8% detected in the 2000-2002 European Community Respiratory Health Survey [6]. Nonetheless, the GA^{2}LEN study showed that ragweed sensitization among outpatients in Europe was increasing and exceeded 2.5% in all countries except Finland [7]. The rates reported for Denmark, Germany, and the Netherlands were 19.8%, 15.2%, and 14.2%, respectively [7].

It is now well-established that ragweed is one of the major causes of allergic rhinitis in the general population in North America. In NHANES 2005-2006, among those who reported hay fever in the past 12 months, the sensitization rate for ragweed was 32.8% [8]. In the French Rhône-Alpes region, up to 12% of the population is allergic to ragweed [9].

A few ecological studies have studied the association between ragweed pollen and pediatric and adult emergency visits or hospitalization for asthma. They have reported both a negative [10-12] and a positive [13] association between ragweed pollen and pollinic asthma. The effects of *Ambrosia* pollen on asthma exacerbation are difficult to assess because of possible confounding by circulating rhinoviruses every September. Another study found that an increase of 72 ragweed pollen grains per cubic meter was associated with an approximate 10% increase in emergency department visits for ocular symptoms among children [14]. Furthermore, 2 studies conducted in Canada found a positive association between ragweed particulate levels and physician visits for rhinitis [15-16]. Few panel studies have investigated the relationship between ragweed pollen counts and hay fever symptoms. One study has shown that ragweed pollen is significantly correlated with asthma and rhinitis symptoms [17], but it did not investigate sensitization to ragweed. Another study has shown that airborne pollen concentrations as low as 6 to 9 grains/m^3 can produce asthma symptoms in the sensitized population [18].

The aim of the present study was to investigate the dose-response relationship between ragweed exposure in patients sensitized to *Ambrosia* and daily hay fever symptoms, using generalized estimating equations (GEE). The effects of airborne pollen levels of *Ambrosia* on daily observations of rhinitis, conjunctivitis, and respiratory symptoms were analyzed using a panel study design, with each individual acting as his or her own control. This instrument is well-known in the study of factors influencing asthma severity [19-20], but to our knowledge, this is the first time it has been used in patients with *Ambrosia* hay fever. This study provides data that will help to provide a better understanding of this emerging allergy in France and to improve patient care.

Materials and Methods

2.1 Study Population and Allergy Testing

The panel study was carried out in 5 towns in France and 1 in Switzerland (Geneva). Each town was equipped with at least 1 pollen trap. Adult patients sensitized to ragweed were recruited. Sensitization was defined as either a positive skin prick test (wheal diameter, ≥3 mm) to ragweed pollen and/or a positive (≥ 0.35 kU/L) in vitro test for specific IgE. Conventional lancet skin prick tests and/or specific IgE measurements using samples of common allergens, namely, ragweed (*A artemisiifolia*), house dust mites (*Dermatophagoides pteronyssinus and Dermatophagoides farinae*), grasses, molds (*Alternaria*), and cat and dog dander were carried out according to international recommendations.

The following eligibility criteria for the study were used: 1) occurrence of seasonal rhinitis in the past 2 years or longer, 2) age of at least 18 years, 3) sensitization to *A artemisiifolia*, 4) residence within 30 km of a pollen trap, 5) current nonsmoker status. The following exclusion criteria were applied: 1) perennial rhinitis; 2) current asthma with daily treatment; 3) sensitization to cat and/or mites with perennial symptoms; and 4) long-term oral corticosteroid treatment.

On inclusion, each physician completed a questionnaire to collect data on demographics, hay fever history, medical history, and medication, and provided the participant with detailed instructions on how to fill in a symptom diary. In addition, each participant completed a self-administered questionnaire on active and passive smoking and typical lifestyle factors that can affect exposure to pollens.

2.2 Symptom Diary

All participants were asked to complete a symptom diary from 13 July to 4 October 2009 and/or from 2 August to 10 October 2010. They were asked to record, each evening, daily nasal, ocular, and bronchial symptoms, respiratory infections, and medication (antihistamines, local treatment for conjunctivitis, rhinitis, and asthma). The severity of eye (itching and/or tear flow and/or conjunctival redness), nose (sneezing and/or runny nose and/or blocked nose) and bronchial (cough and/or wheezing and/or asthma) symptoms was recorded on a 4-point scale (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; 3, severe symptoms). Quality of health was assessed by the patients using an analog scale ranging from 0 (poor health) to 10 (excellent health). The diaries had to be sent in every Monday and were checked at reception. If the diaries were not returned or if there were any incorrect answers, the individuals were contacted by phone. The study was approved by CCTIRS (*Comité Consultatif sur* *le Traitement de l'Information en matière de Recherche de la Santé*) and all participants gave written informed consent.

2.3. Pollen Data

Daily ragweed pollen levels were drawn in each town from the National Aerobiological Network Survey (RNSA) and by MeteoSwiss for Geneva. Measurements were made using a Hirst-type pollen trap (Burkard Manufacturing Co Ltd or Lanzoni) that was located 15 meters above ground level. This method involves drawing 10 liters of air per minute continuously onto a tape coated with adhesive. Particles in the air stick to the tape, which moves past the inlet at 2 mm per hour to give a time-related sample. The pollen is then identified and quantified by a trained palynologist and related to the volume of air averaged over 24 hours.

2.4. Air Pollution and Meteorological Data

Air pollution data were obtained in each French town from the BDQA (Databank on Air Quality) managed by the French agency ADEME (*Agence De l'Environnement et de la Maîtrise de l'Energie*). For Geneva, they were obtained from Transalpair. Average daily concentrations of nitrogen dioxide (NO_2) and particles with a median diameter of 10 microns or less (PM_{10}) were used in the study as well as daily maximum 8-hour average ozone (O_3) concentrations. However, only PM_{10} and O_3 concentrations were used for analysis. Meteorological data (daily maximum temperature, average relative humidity, wind speed, rainfall, and atmospheric pressure) were measured in each town by the respective national meteorology services (Météo-France and MeteoSwiss).

2.5 Statistical Methods

For each nasal, ocular, and respiratory symptom, daily scores were transformed into a dichotomous response variable: "no symptoms" for mild or no symptoms (score, $\leq$1) and "symptoms," for moderate or severe symptoms (score, >1).

A 2-stage modeling approach was applied with an appropriate model for repeated data, GEE, using an exchangeable correlation matrix, with the Genmod procedure in SAS [21]. First, the linearity of the pollen-symptom relationships was checked graphically by dividing the pollen variable into 10 classes and calculating odds ratio (ORs) for each class. Then, if the relationship was linear, the pollen level was introduced into the GEE model as a quantitative variable; otherwise piecewise GEE regression was performed with 2 quantitative pollen variables: one ranging from 0 to the saturation point and the other ranging from the saturation point to the maximum point. The pollen-symptom relationship was quantified by calculating ORs for an increase of 10 grains of pollen/m^3.

Confounding variables were chosen to avoid highly correlated variables. Maximum temperature, mean relative humidity, wind speed, O_3, and PM_{10} were selected together with participant age. Two-time trend variables were introduced: month ("0" for the first half of the period, ie, 13 July-23 August 2009 and 2 August-6 September 2010, and "1" for the last half of the period, ie, 24 August-4 October 2009 and 7 September-10 October 2010) and weekend ("1" for Saturday and Sunday vs "0" for all other days). This last variable was introduced to account for the fact that people perform different activities (eg, more outdoor activities) at weekends. A year variable was also created: "0" for 2009 and "1" for 2010 to take into account variations between the pollen seasons 2009 and 2010. Three different lags were tested: "0" (same day pollen), "1" (day before pollen) and "01" (average of these 2 days), and the result with the most significant lag was retained. Weather and pollution variables were introduced into the model with the same lag as pollen. Interactions between the independent variables of the model were tested and retained when significant. Treatment was added to the model in a sensitivity analysis to assess the relative influence of treatment and pollen on symptoms.

Results

3.1 Population Studied

3.1.1 Panel Participation

For the panel study, 31 adults with ragweed allergy were included: 16 in 2009 and 22 in 2010. Of these 31 patients, 7 participated in the 2 years. One participant was excluded because he failed to provide the requested daily health records during the month of August and additionally he experienced hay fever before the pollen season. Thus, our analyses are based on data from 30 participants.

3.1.2 Panel Description

Table 1 shows the general social, demographic, and clinical characteristics of the population. The mean (SD) age of the study population was 39.6 (10.8) years; the mean age at onset

Table 1. Characteristics of Sampled Population (n=30)[a]

Sex	
Female	22 (73.33)
Male	8 (26.67)
Active smoking	
Nonsmoker	21 (70)
Ex-smoker	8 (26.66)
Smoker	1 (3.33)
Passive smoking	
No	26 (86.67)
Yes	4 (13.33)
Animals	
No	20 (66.67)
Yes	10 (33.33)
Age, mean (SD), y	39.6 (10.76)
Sensitization to Ambrosia artemisifolia	
IgE	21 (70)
Skin prick test	9 (30)
Active asthma (asthma symptoms in last 12 months)	
No	27 (90)
Yes	3 (10)

[a]Data are shown as number (%) of patients unless otherwise specified.

Table 2. Ragweed Pollen Counts in 2009 and 2010

	Town	No. of Days	Mean Grains/m^3	SD	Minimum Grains/m^3	Median Grains/m^3	Maximum Grains/m^3
2009	Avignon	77	6.6	10.2	0	3	47
	Lyon	84	13.0	25.2	0	2	152
	Nevers	83	12.4	24.13	0	2	137
2010	Avignon	70	5.9	10.6	0	2	59
	Lyon	70	33.5	87.5	0	8	543
	Nevers	70	16.1	34.7	0	3	205
	Geneva	69	3.2	8.6	0	0	54
	Grenoble	70	3.0	5.3	0	1	20
	Saint-Étienne	69	2.0	4.8	0	1	31

of hay fever was 26.8 (12.3) years; and the mean duration of hay fever at the time of the study was 12.8 (10.0) years.

3.2 Environmental Data

Table 2 shows the ragweed pollen counts in the Rhône-Alpes region and its surroundings. The 2 pollen seasons were markedly different. Due to intense *Ambrosia* pollination in 2010, the total load of *Ambrosia* pollen was higher than in 2009, especially in Lyon (63% of participants) (2305 vs 1105).

3.3 Variations in Ragweed Pollen Counts and Percentage of Patients With Symptoms (Figure)

The volunteers presented nasal symptoms on 70% of the days studied in 2009 and on 72% of the days studied in 2010. These symptoms were qualified as moderate or severe for 35% of the days in 2009 and for 31% in 2010. Ocular and respiratory symptoms were less frequent than nasal symptoms and were also less frequent in 2010 than in 2009.

3.4 Relationship Between Ragweed Pollen Counts and Symptoms

We observed a linear relationship between symptoms and ragweed pollen counts. Table 3 shows the results of the GEE model.

3.4.1 Nasal Symptoms

There was a significant and positive relationship between nasal symptoms and the concentration of airborne ragweed pollen. Two significant interactions were detected: pollen and year and pollen and weekend. This relationship was stronger in 2009 and at weekends. For every increase of 10 grains/m^3, the OR for nasal symptoms in 2009 was 1.18 [1.04-1.35] on weekdays and 1.43 [1.16-1.75] at weekends. In 2010, it was 1.04 [1.00-1.07] on weekdays and 1.25 [1.06-1.46] at weekends.

3.4.2 Ocular Symptoms

For every increase of 10 grains/m^3, the OR for ocular symptoms was 1.32 [1.16-1.56] in 2009 and 1.05 [1.02-1.07] in 2010.

3.4.3 Respiratory Symptoms

There was a significant and positive relationship between respiratory symptoms and concentrations of ragweed pollen in 2009. In 2010, the relationship was also positive but not statistically significant. For every increase of 10 grains/m^3 of pollen, the OR was 1.14 [1.03-1.25] in 2009 and 1.03 [0.97-1.08] in 2010.

3.5 Treatments (Table 3)

The participants received antihistamine therapy on 30% of the days studied in 2009 and on 42% in 2010. They received local therapy for hay fever on 38% of the days in 2009 and on 44% in 2010. Treatment use increased with pollen counts during the ragweed pollen seasons.

When we introduced antihistamines and local therapy into our models, the relationship between pollen concentration and nasal symptoms decreased but remained significant for weekends. In 2009, the OR for nasal symptoms was 1.13 [0.99-1.28] on weekdays and 1.33 [1.07-1.65] at weekends. In 2010, it was 1.02 [0.98-1.05] and 1.20 [1.00-1.44], respectively. The relationship between symptoms and treatments was positive and significant, with ORs of 2.35 [1.24-4.45] and 2.97 [1.65-5.35] respectively for the relationships nasal symptom-antihistamine therapy and nasal symptom-nasal spray.

Discussion

There is a linear relationship, without thresholds or plateaus, between the level of airborne ragweed pollen and nasal, ocular, and respiratory symptoms. Nasal symptoms differ from year to year and also within the week.

Our study shows that nasal symptoms differ between weekdays and weekends. As shown by Parisi et al [22], UV exposure, expressed as a percentage, was consistently higher at weekends than during the week. It would appear logical that people spend more time outdoors at weekends compared to weekdays, when they usually work indoors. As shown in a Finnish study, adults aged 30 to 45 years took significantly more aerobic steps (continuous walking of at least 10 minutes'

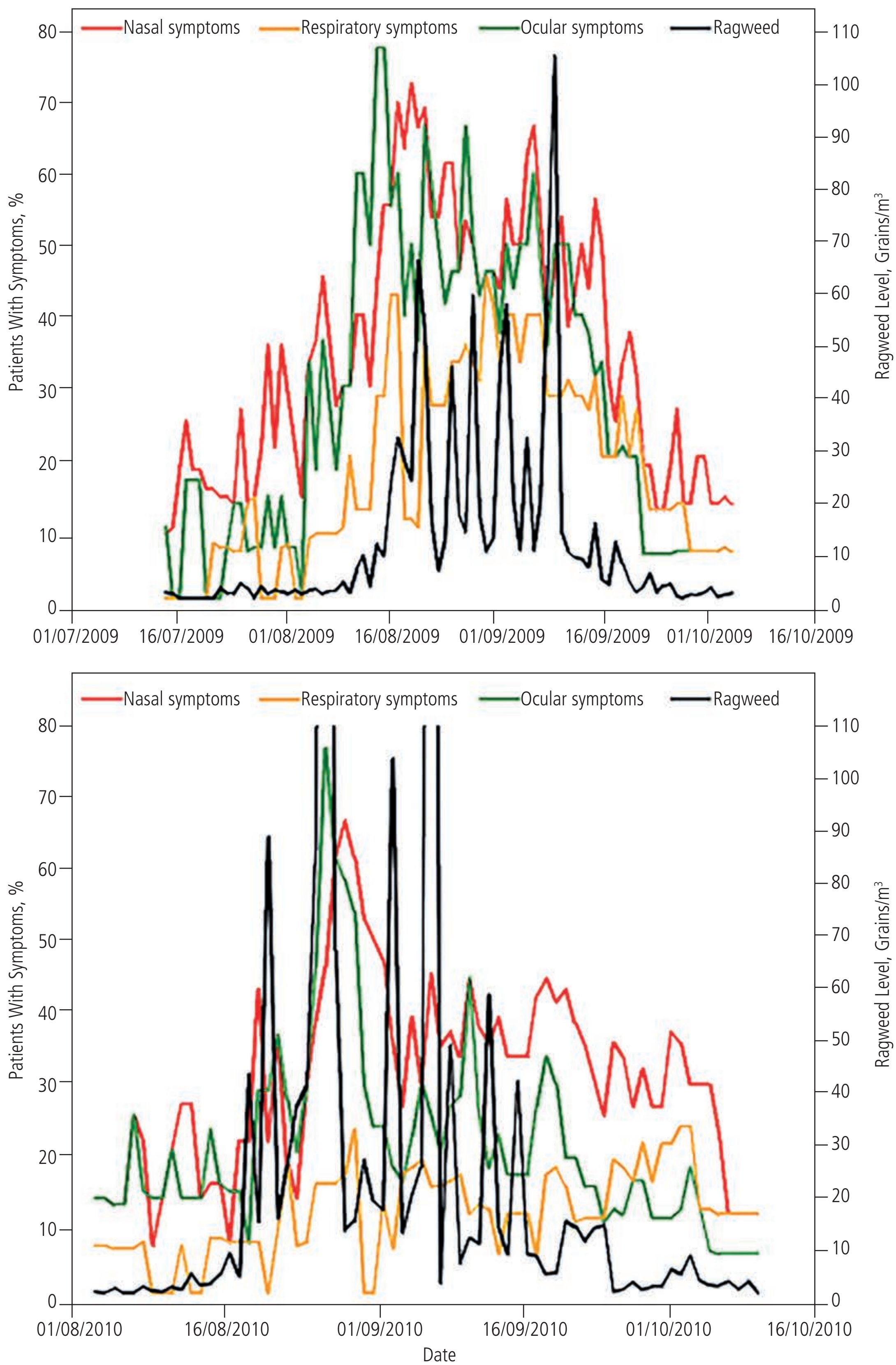

Figure. Variations in ragweed pollen counts and percentage of patients with symptoms in 2009 and 2010.

Table 3. Relationship Between Ragweed Pollen Counts and Hay Fever Symptoms

	No. of Days	Year	Nasal Symptoms (Weekdays)		Nasal Symptoms (Weekends)		Ocular Symptoms		Respiratory Symptoms	
			Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Complete model	2313	2009	1.18[a]	(1.04-1.35)	1.43[a]	(1.16-1.75)	1.32[a]	(1.16-1.52)	1.14[a]	(1.03-1.25)
		2010	1.04[a]	(1.00-1.07)	1.25[a]	(1.06-1.46)	1.05[a]	(1.02-1.07)	1.03	(0.97-1.08)
Treatment	2313	2009	1.13	(0.99-1.28)	1.33[a]	(1.07-1.65)	1.26[a]	(1.11-1.43)	1.12[a]	(1.01- 1.25)
		2010	1.02	(0.98-1.05)	1.20[a]	(1.00-1.44)	1.04[a]	(1.01-1.07)	1.02	(0.97- 1.08)

[a]Significant results.

duration at a pace of 60+ steps/min) on a weekend day than on a weekday ($P<.001$) [23]. It would be interesting to study the influence of daily activities of participants on hay fever symptoms.

Total ragweed pollen load was higher in 2010 than 2009, especially in Lyon. The percentage of individuals without moderate or severe symptoms was, however, 23% lower in 2010. This contradiction between the severity of symptoms and total pollen sums may be related to the allergen content of pollen grains, which possibly vary considerably from year to year, as reported for birch pollen grains by Buters et al [24-25]. It might also be related to the different nature of the 2 pollen seasons. The 2 sets of individuals in consecutive years may also have been somewhat different with respect to sensitivity to ragweed pollen [26].

We did not observe a priming effect at the beginning of the season. This is in contrast to observations by Connell [27] in experimental conditions with ragweed and to the more recent findings of an epidemiological panel study of patients sensitized to Poaceae [28]. Grammer et al [29], however, reported absence of nasal priming during natural ragweed exposure in allergic rhinitis patients. The lack of a sufficient number of patients to allow the detection of a strong statistically significant relationship may also explain the absence of priming in our study.

When we added treatments to our analysis, the relationship between pollen counts and symptoms decreased and lost its statistical significance for weekdays. We noted a positive, statistically significant relationship between the use of antihistamine therapy and local therapy for hay fever symptoms, demonstrating that treatment use reflects the severity of symptoms. The treatments analyzed have been shown to be therapeutically effective [30].

There are some limitations to our study. It would have been preferable to include patients who were strictly monosensitized to *A artemisiifolia* in order to obtain more accurate results regarding the relationship between pollen exposure and symptoms [31]. However, due to the rarity of monosensitized patients, the study had to include polysensitized patients. Pollen exposure was based on data from a single pollen sampler in each town. A single collector can nevertheless reflect temporal variations in pollen concentrations for a given species within a 30-km radius [32], and although rooftop pollen counts do not fully reproduce human exposure at street level, personal exposure to pollen correlates well with stationary measurements used to report pollen counts [33]. Stationary measurements were used to assess air pollution. Studies on exposure to air pollution have shown that the correlation between personal exposure and stationary measurements is better in longitudinal studies than in cross-sectional studies [34]. This study did not collect information on fungal spore sensitization or the presence of spores, which may produce hay fever symptoms. Nevertheless, sensitization to molds is rather low in French adults [6] and children [35]. Finally, our patients might not represent the general population with ragweed hay fever, but rather, patients with severe symptoms, typically seen by allergists [36].

Conclusions

There is a statistically significant relationship between ragweed pollen counts and hay fever symptoms. Our study shows that nasal symptoms differ from year to year and from weekdays to weekends. We did not detect a threshold. It would be interesting to conduct a larger study capable of detecting a potential threshold and of confirming the differences observed between weekdays and weekends in order to adjust symptomatic treatment accordingly.

Acknowledgments

The French Aerobiology Network: Barriere C (Nîmes), Bataille A (Nantes), Boix-Suard F (Angers), Bonneau JC (Angers), Carre Faure Mc (Tours), Chapuis N (Rochefort), Chateau-Waquet D (Paris), Chevallier D (Nantes), Cheynel A (Chambéry), Dubreil Y (Nantes), Epstein M (Paris), Fabre C (Bagnols-sur-Cèze), Gumowski P (Geneve), Jezraoui Benabes B (Amiens), Jonathan AM (Sevres), Larcheveque M (Rouen), Merabat-Feral R (Chalon/s/Saone), Noualhaguet C (Bois d'Arcy), Nozick M (Chelles), Prezelin N (Nantes), Rey Nunez ML (Montreuil), Riotte Flandrois F (Péage de Roussillon), Roig P (Suresnes), Schwender D (Dijon).

Funding

This study was supported by grants from ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail): research convention number EST 2008/1/21.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received May 6, 2013; accepted for publication, September 13, 2013.

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