

Received Date : 25-Aug-2016

Revised Date : 23-Jan-2017

Accepted Date : 11-Feb-2017

Article type : Original Article: Experimental Allergy and Immunology

Handling AE: Wytske Fokkens

Allergic respiratory disease: different allergens, different symptoms

Authors: Antonio Valero¹, Santiago Quirce², Ignacio Dávila³, Julio Delgado⁴, Javier Domínguez-Ortega²

1. Pneumology and Allergy Department; Clinical and Experimental Respiratory Immunoallergy, IDIBAPS; CIBERES; Hospital Clinic, Barcelona
2. Department of Allergy. Healthcare Research Institute IdiPAZ. CIBER de Enfermedades Respiratorias, CIBERES. Hospital Universitario La Paz. Madrid.
3. Immunoallergy Department. IBSAL-Hospital Universitario de Salamanca.
4. Allergy Department. Hospital Virgen Macarena. Sevilla

Corresponding author: Dr. Antonio Valero Santiago

Pneumology and Allergy Department; Clinical and Experimental Respiratory Immunoallergy, IDIBAPS; CIBERES; Hospital Clinic, Barcelona

Telephone: (+34) 932275500

Electronic mail: valero@clinic.ub.es

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.13141

This article is protected by copyright. All rights reserved.

Abstract

Background: Spanish population is rather homogeneous in its genetic and socio-cultural characteristics, but allergen sensitization shows wide geographical variations. We aimed at assessing whether sensitization to different allergens in the diverse geographical areas induced different clinical and quality of life characteristics in adult patients with a first-time diagnosis of rhinitis and/or asthma.

Methods: Two sequential, identically designed studies were carried out to evaluate such associations (PERFILAR I and II). PERFILAR II was an extension of PERFILAR I with additional allergens being included. Both phases were epidemiological, descriptive, cross-sectional, non-intervention multicenter studies. Participants were required to have lived for at least the last 2 years in the geographical zone. Asthma control assessment was based on ACQ5. Health-related quality of life was evaluated with validated scales for rhinitis (ESPRINT-15) and asthma (Mini-AQLQ). Skin prick tests were used to identify sensitization to involved allergens.

Results: 301 physicians recruited 2711 patients for PERFILAR I+II. Sensitization to allergens was significantly different in patients with rhinitis with/without asthma. Seasonal allergens were associated with rhinitis, a longer time to asthma development, and more severe and commonly intermittent rhinitis. HDM were associated with more common rhinitis, and *Alternaria* was associated with asthma. The study confirms an association of geographical areas with relevant allergens and allergic clinical picture.

Conclusion: Different types of aeroallergens and specific sensitization profiles are associated with different allergic clinical pictures (rhinitis with/without asthma), different clinical symptoms and severity. This could have implications to predict later clinical course and to select appropriate management approaches.

Keywords

aeroallergen, asthma, geographical variation, rhinitis,

Introduction

Allergy is a systemic hypersensitivity reaction, immunologically-mediated, with an impact on various organs, particularly those being part of the respiratory system. The allergic reaction is triggered by environmental allergens and results in IgE production in susceptible individuals.^{1,2} Symptoms and signs are due to an IgE-mediated reaction, resulting in an inflammatory process.

Allergic rhinitis is the most common respiratory allergic disorder and is usually associated with conjunctivitis and/or asthma, occurring after mucosal membranes exposure to aeroallergens. Estimated prevalence of rhinitis in general population is 10-30% worldwide³ and up to 42% in some developed countries.⁴ In Spain, estimated prevalence is 22%.⁵ Asthma prevalence is 4-10% at a global level,^{3,6} and 7% in Spain.⁷ As stated in current guidelines, a clear association exists between both disorders;⁸⁻¹⁰ they are known to occur concurrently resulting from a common pathogenic process causing a chronic respiratory inflammation.¹¹ Available data suggest that between 20-50% of patients with allergic rhinitis have asthma¹² and between 30-90% of asthmatic patients have rhinitis.¹² Similar results have been published in the Spanish allergic population^{13,14}

Depending on the involved allergens, symptoms can be seasonal (usually appearing over a 2- to 3-month pollen season, for grass, trees, and weed pollen; or fungi) or perennial with slight seasonal variations (house dust mites [HDM] and dog/cat dander). Sensitization to such allergens is very common, and exposure level has some influence on rhinitis and asthma symptoms in sensitized individuals. Involved allergens vary in different populations, depending on climatic and environmental factors. European Community Respiratory Health Study reported a marked geographical variation both in relevant allergens and in allergic symptoms and disorders.¹⁵⁻¹⁷ In Spain, main allergens causing allergy in Eastern coastal area and Canary Islands are HDM, whereas in Southern areas the most relevant allergen is olive pollen, and in Northern and Central areas the most common one is grass pollen. In a pediatric study,

sensitization to HDM was 83% in coastline, whereas at 5-30 km inland half reduced such proportion; *Alternaria* allergen showed a reverse pattern.¹⁸

In spite of the association of allergen sensitization to allergic rhinitis and/or asthma, available studies on the association of specific kinds of allergens to clinical symptoms, severity, or therapy for respiratory allergic diseases are very limited. However, in a cross-sectional study in Chinese allergic patients, sensitization to *Artemisia vulgaris* and *Ambrosia artemisifolia* was found to be associated with the severity of intermittent rhinitis, whereas sensitization to HDM (*D. pteronyssinus* and *D. farinae*) was associated with severity of asthma.¹⁹

Spanish population is rather homogeneous in its genetic and socio-cultural characteristics all over the country, but allergen sensitization shows wide geographical variations. This allows carrying out studies on the association of relevant allergens to clinical features of allergic respiratory diseases, and to their well-known effects on health-related quality of life; this could have also an impact on therapy selection for such patients.

Two sequential, identically designed studies were carried out to evaluate such associations. In PERFILAR I^{20,21} several selected allergens were investigated and associated differences were found in clinical features, diagnostic methods and therapies,²¹ as well as differences in health-related quality of life scales scores,²⁰ depending on relevant allergens. PERFILAR II was an extension of PERFILAR I with additional allergens being included. A combined analysis of both studies is presented.

The main purpose was to assess whether sensitization to different allergens in the diverse geographical areas induced different clinical and quality of life characteristics in adult patients with a first-time diagnosis of rhinitis and/or asthma.

Material and methods

Both phases (PERFILAR I and II) were epidemiological, descriptive, cross-sectional, non-intervention multicenter studies. Studies were approved by the Ethics Committee in Hospital Clinic, Barcelona, Spain.

Patients aged 18 or older, with a first-time diagnosis of respiratory allergy (rhinitis with or without asthma, according to updated ARIA guidelines for rhinitis ⁸ and GEMA guidelines for asthma ¹⁰) due to relevant allergens being investigated in each phase were included. Physicians classified patients into different groups according to their profile of allergy to perennial or seasonal allergens. Sensitization was confirmed by a positive skin prick test and/or the determination of specific IgE (ImmunoCAP, ThermoFisher Scientific, Sweden). Many atopic patients develop sensitization to several allergens without clinical manifestations, and thus, polysensitized patients were not necessarily polyallergic according to their clinical history.²² In order to establish the clinical relevance of pollen and dander sensitization, there should be a documented history of consistent symptoms during the allergen exposure period for each seasonal allergen, and continuous presence of exposure to pets in the case of allergy to animal dander. For HDM and *Alternaria*, all included subjects presented with persistent perennial symptoms consistent with HDM and molds exposure, respectively. Patients co-sensitized to other potential allergen that could influence the clinical picture in a specific period were not included in the study. To exclude polyallergy to different pollen types, a patient allergic to one seasonal allergen could not be assigned to other group. Patients with other lung or nasal disorders, those having received immunotherapy in the past, or sensitized to occupational or other environmental allergens not evaluated in the study were excluded. Participants were required to have lived for at least the last 2 years in the geographical zone in which they were being recruited and to have granted their written informed consent.

PERFILAR I was carried out from January to June 2010 in patients sensitized to grass pollen, olive pollen (patients included from March to June, i.e. the pollen season in Spain), or HDM.

PERFILAR II was conducted from March 2011 to March 2012 in patients sensitized to cypress (Cupresaceae), plane tree (*Platanus*), or *Parietaria* pollen, *Alternaria* spores, or dog and/or cat dander.

Both studies were conducted in allergy clinics from all the different geographical areas in Spain²¹. A total 200 allergists participated in the study. Each investigator was to recruit six consecutive patients and to enter themselves data from the patients on a structured case report form (supplementary file). Recorded data included: socio-demographic characteristics (age, sex, smoking habit, body mass index [BMI], and place of residence), previous familial and medical history, current symptoms and signs, diagnostic tests, prior therapies, and therapies being prescribed during the inclusion/assessment visit. Rhinitis was diagnosed and classified based on ARIA guidelines⁸ using the modified version developed by Valero et al.²³ Spanish GEMA guidelines¹⁰ were used for asthma diagnosis and classification, and for asthma severity and asthma control degree in inclusion/assessment visit. Asthma control assessment was based on Asthma Control Questionnaire ACQ5 (Controlled (ACQ-5 <0.75); partially controlled (ACQ-5 > 0.75 and < 1.5); uncontrolled (ACQ-5 >1.5))²⁴. Health-related quality of life (HRQOL) was evaluated with a specific scale for rhinitis (ESPRINT-15; scores range between 0 (no limitation) and 6 (maximum limitation)) that has been validated in Spain²⁵ and a specific questionnaire for asthma (Mini-AQLQ; scores range between 1 (maximum limitation) and 7 (no limitation)²⁶ also validated for Spanish population.²⁷ Patients fulfilled these questionnaires directly by themselves.

Skin prick tests were used to identify sensitization to involved allergens. Specialized nurses performed the tests but results were also evaluated by the investigators. Histamine (10 mg/mL) was used as a positive control and 0.9% saline was used as a negative control. A positive result was defined as a wheal of >3 mm larger than with negative control. In some patients, specific serum IgE immunoglobulin was also assessed (ImmunoCAP, Phadia, Sweden) with a value > 0.35 kU/L being taken as a positive result for any allergen.

Statistical analyses were performed with SAS ® version 9.3 statistical package. All patients providing data were included in the analysis population. Summary descriptive statistics for the whole sample and for allergen subgroups were presented, and results were stratified for rhinitis and/or asthma diagnoses. Categorical variables were described by number and proportion; and continuous variables were presented with mean and standard deviation or median and interquartile range, depending on their normal or non-normal distribution. No imputation was used for missing data. Association of clinical characteristics to sensitization to eight allergens (olive, grass, cypress [Cupresaceae], plane tree [*Platanus*], or *Parietaria* pollen; *Alternaria* spores; HDM; and dog and/or cat dander) was investigated. Furthermore, perennial allergens (HDM, dander, *Alternaria*) were compared with seasonal (cypress, grass, olive, *Platanus*, *Parietaria*) allergens. Associations between categorical variables were assessed with contingency tables and chi-squared tests or Fisher exact tests, as required. Continuous variables were assessed with Student t test or ANOVA for normally distributed variables, and non-parametric Wilcoxon or Kruskal-Wallis test for non-normal variables. Correlations between continuous variables were measured with Pearson or Spearman coefficients. Statistical significance was defined as $p < 0.05$.

Logistic regression models were estimated to assess factors independently related to patient's sensitization profile. The following outcomes were considered for the three primary analyses: Sensitization to perennial/seasonal allergens; in perennial allergens sensitized patients, *Alternaria*/dander/HDM; and in seasonal allergens sensitized patients, Cypress/grass/grass plus olive/olive/*parietaria*/plane tree.

Associated covariates have been identified among the following list of variables: age (years), gender (male/female), BMI (Kg/m^2), geographical zone (coast/inland), place of residence (rural/semiurban/urban), severity of rhinitis (no rhinitis or mild/moderate/severe), severity of asthma (no asthma/intermittent/mild persistent/moderate persistent/severe persistent) and presence of concomitant allergic diseases [i.e. conjunctivitis (yes/no), atopic dermatitis (yes/no), food allergy (yes/no), drug allergy (yes/no) and allergy to hymenoptera (yes/no)]. A stepwise

procedure was carried out to select the best model using a significance level criterion for variable entry of 0.3 and of 0.05 for variable removal (based on the Wald test for parameter effect). Interaction between the independent variables was not considered.

Results

Three-hundred and one physicians recruited 1437 patients for PERFILAR I and 1274 for PERFILAR II. Geographical distribution of participating centers in areas with different prevailing allergens in Spain is shown in Figure 1. Out of 2711 patients, 92.5% (2507) met all inclusion criteria and were considered to be eligible (1482 [59.1%] with rhinitis without asthma, 944 [37.7%] with rhinitis and asthma, and only 81 [3.2%] with asthma alone). Duration of rhinitis and asthma (mean $\pm$ SD) was 7.3 ± 7.7 and 6.2 ± 7.9 years, respectively. Time to asthma development since rhinitis onset was 2.3 ± 4.2 years.

Demographic data and diagnoses are shown in Table 1. Mean age was 35.0 ± 11.3 years, with women (54%) slightly outnumbering men. A majority of patients lived in urban areas (73.2%) and in non-coastal regions (69.2%), and were referred by primary care centers (86.9%). The proportion of patients living in non-coastal areas was higher among patients with rhinitis and asthma than in patients with rhinitis without asthma (74.2% vs 65.9%, $p < 0.001$). Almost half of patients reported a family history of atopy in first-degree relatives; a family history of atopy was more common in patients with rhinitis and asthma than in patients with rhinitis without asthma (45.6% vs. 54.7%, $p < 0.0001$). Other concurrent allergic diseases were also more common in patients with rhinitis and asthma (atopic dermatitis 14.6% vs. 10.4%, $p = 0.0094$; food allergy 13.7% vs. 8.8%, $p = 0.0011$; drug allergy 8.0% vs. 5.5%, $p = 0.0016$), except for conjunctivitis (75.2% vs. 76.0%). HRQOL score for rhinitis (ESPRINT-15) was 2.41 ± 1.31 , with scores being significantly higher in patients with rhinitis and asthma than in patients with rhinitis without asthma (2.36 ± 1.29 vs. 2.48 ± 1.33 , $p = 0.0181$). HRQOL score for asthma (Mini-AQLQ) was 4.96 ± 1.23 . Asthma score in ACQ-5 was 1.63 ± 1.20 with 49.9% of patients

showing uncontrolled asthma. Baseline clinical and quality of life characteristics of patients are shown in Tables 2 and 3, respectively.

Prevalence of sensitization to relevant allergens in patients with rhinitis with/without asthma is shown in Figure 2. Distribution was significantly different in both groups ($p < 0.0001$).

Clinical characteristics and quality of life according to type of involved perennial or seasonal allergens is shown in Table 4. Seasonal allergens were associated with rhinitis ($p < 0.0001$) and to a longer time to asthma development since rhinitis onset ($p < 0.0003$). Moreover, in patients sensitized to seasonal allergens, rhinitis was more severe ($p < 0.0008$), and was more commonly intermittent ($p = 0.0031$). Disturbing symptoms, daily activities limitations and poorer school/work performance, as per ARIA assessment, were significantly more common with seasonal allergens.

Even though asthma tended to be less severe in patients sensitized to seasonal allergens ($p = 0.0243$), no significant differences were observed in the proportion of patients with adequately controlled asthma (based on ACQ-5). Concurrent allergic diseases were common. As expected, conjunctivitis was significantly more common for seasonal allergens ($p < 0.0001$). Food allergy was also more common for seasonal allergens ($p = 0.0488$), whereas drug allergy was more common for perennial allergens ($p = 0.0026$). HRQOL measures associated with rhinitis (ESPRINT-15) and asthma (Mini-AQLQ) did not show any significant difference between both allergen types. A logistic regression analysis showed a significant association of seasonal allergens to older age ($p < 0.0001$), men ($p = 0.0004$), non-coastal place of residence ($p < 0.0001$), severe rhinitis ($p = 0.0008$), mild asthma ($p < 0.0001$) and concurrent conjunctivitis ($p < 0.0001$).

Comparative analyses of clinical characteristics and quality of life by specific allergens are shown in Table 5 (perennial allergens) and 6 (seasonal allergens). In patients sensitized to perennial allergens, HDM were associated more frequently with rhinitis, and *Alternaria* was associated with asthma, whereas animal dander did not show a clear-cut trend ($p < 0.0001$).

Accepted Article

Duration of rhinitis and asthma was longer in patients sensitized to *Alternaria* ($p = 0.0490$ and $p = 0.0282$, respectively). Allergy was more commonly associated with intermittent rhinitis ($p = 0.0311$). In patients with asthma, disease control was more common for HDM ($p = 0.0287$). Conjunctivitis was more common for animal dander allergy ($p = 0.0409$) and drug allergy was more common for *Alternaria* ($p = 0.0309$). No differences were found among allergens in HRQOL. In patients sensitized to seasonal allergens (Table 6), significant differences were found for rhinitis and asthma occurrence and for disease duration and some symptoms and HRQOL scores, but no integrative patterns could be discerned. However, among the seasonal allergens, *Olea* pollen sensitized patients had greater effects on their HRQoL, both in patients diagnosed with rhinitis, as in those diagnosed with asthma and rhinitis (Table 6).

Based on the results of the regression models, aging is a factor related to seasonal allergens and especially to cypress. A worst severity of rhinitis and the presence of conjunctivitis are factors related to seasonal allergens too. On the other hand, a worst severity of asthma is related to perennial allergens and especially to *alternaria*. The geographical zone had also an influence on the sensitization profile, being the coast zone more related to the sensitization to HDM, olive, parietaria and plane tree. Living in a rural environment is also related to the sensitization to parietaria. Results from logistic regression models are shown in Figures 3-5.

Discussion

In this large study from multiple geographical areas (see Figure 1). We found statistically significant differences depending whether patients were allergic to seasonal allergens or to perennial allergens. Thus, allergic rhinitis was more frequent in to seasonal allergen allergic patients whereas asthma was more frequent in perennial allergen allergic patients (PAAP). In addition, time to asthma development since rhinitis onset was higher in SAAP. Also,

intermittent rhinitis was more frequent in SAAP, whereas asthma was more frequent in PAAP. Finally, conjunctivitis and food allergy was more frequent in seasonal allergen allergic. There were no differences in QoL in rhinitis or asthma or asthma control between seasonal and perennial allergen allergic.

Studies trying to correlate clinical characteristics with the type of allergen eliciting sensitization and symptoms are scarce and with a limited number of patients. A number of studies have been performed in China,¹⁹ Africa,²⁸ Latin America;²⁹ and Turkey;³⁰ and also in Western countries such as Finland³¹.

A high proportion of patients suffering from both rhinitis and asthma (37.7%) was found in our study, which supports the notion of a common underlying process.^{11,32} Rhinitis without associated asthma was more frequently associated with seasonal allergens, whereas rhinitis with concomitant asthma was more associated with perennial allergens (see Table 4). Indoor allergens are highly relevant to the development for asthma and asthma morbidity.³⁴ However, in this study, we found differences in the percentage of allergic rhinitis patients that suffered from asthma between seasonal and perennial allergens. These differences seem to be related to *Alternaria* and animal dander sensitization, but not to HDM sensitization (see Figure 2). This could be related to the pattern of exposure in Spain: HDM are not relevant sensitizers in several regions of Central Spain, while moulds and pets are sensitizers distributed in all territories. A pet cat or dog at home have been associated with high levels of allergen exposure and increases in nonspecific airway hyperreactivity.³³ Unfortunately, we could not establish whether or not our results might be influenced by high levels of exposure, because inclusion criteria included clinical relevance of the allergen but specific information about the number of animals at home or time in contact with pets was not recorded. However, other studies suggest a lack of a direct association between allergen exposure and sensitization, and other environmental adjuvants may contribute through a more complex pathway to sensitization.³⁴ On the other hand, there is a significantly longer difference in the time to asthma development since the onset of rhinitis in

patients with seasonal allergens. This could be explained by a lower demand for consultation in patients exposed to pollens, with symptoms limited to only a few months, while patients with allergy to perennial allergens, whose exposure is more constant, would develop more persistent and intense symptoms resulting in an earlier detection. Association with other allergic diseases, particularly conjunctivitis, was common (73.8%) as reported by others³⁵, and was significantly higher for seasonal allergens.

PERFILAR study has shown a higher rate of persistent symptoms in allergic rhinitis (Table 4) compared with previous results in general population in a cross-sectional study in Western Europe (29% persistent)³⁶ and so similar to those obtained in a cross-sectional study in Spain and Portugal (36% intermittent).³⁷ It is important to note that intermittent vs. persistent rhinitis is not synonymous of seasonal vs. perennial rhinitis. Although intermittent rhinitis is significantly more common in rhinitis induced by seasonal allergens than in allergic rhinitis to perennial allergens, more than 60% of pollen allergic patients suffer from a persistent rhinitis, which confirms that also a great number of patients sensitized to seasonal allergens suffer from mostly moderate [OR: 1.723 (95%CI. 1.296-2.289, p=0.0008] but also from a severe rhinitis. Conversely, in this study exposure to a perennial allergen as dander was more commonly associated with intermittent rhinitis. However, this data might be biased because the mildest cases of pollen allergy could not attend specialist clinics and present results are based on patients attending allergy clinics, not on general population with allergic rhinitis. Regarding severity of rhinitis due to pollen sensitization by different allergens, there was a higher rate of persistent rhinitis in olive, olive and grass, and *Parietaria* allergic patients, probably in concordance to a longer pollen season for those pollens in Spain, which confirms those results previously described in Italy by Milani et al³⁸.

Asthma tended to be more severe in patients sensitized to perennial allergens but we have not found differences by allergens, with the exception of a less intermittent asthma in *Alternaria* allergic patients. On the other hand, although 40% of the asthmatic patients in the global population reach an adequate asthma control according to guidelines criteria, ACQ-5 reduces

that level to 29%. As it has been recommended, an objective tool to assess asthma control should be used in clinical practice to avoid bias by doctor's or patients' perception.³⁹ Interestingly, there have been no differences in controlled asthma between seasonal or perennial allergens. When comparing perennial allergens, *Alternaria* allergic asthmatic patients show a worse level of controlled disease (based on GEMA guidelines) in concordance to previous reports in adults.⁴⁰ In fact, fungal sensitization has been associated with increased asthma morbidity and mortality, including higher rates of hospitalization.⁴¹ Conversely, in seasonal allergic asthma, olive allergic patients had a worse mean ACQ-5 result with a higher uncontrolled patient's proportion. It is remarkable that pollen can reach high environmental concentrations exceeding the threshold level above which most people sensitized to a pollen develop symptoms related to the disease in a short time, but pollen exposure could also be associated with an epidemic increase in asthma episodes coinciding with very high atmospheric pollen counts.⁴² This effect might explain the worst mean results in ACQ-5 for allergic people to olive and grass and olive pollens at the same time. Sensitization to olive pollen is also an important cause of pollinosis in Mediterranean countries and grasses and olive trees pollinate approximately at the same time in Spain. Brito et al previously described that asthma symptoms showed positive and significant correlations with olive pollen counts ($r = 0.700$, $p < .001$) and aeroallergen levels ($r = 0.803$, $p < .001$).⁴³ However, for cypress pollen, although there are significantly less patients with asthma as compared to other pollens, as it was previously described in Spain,⁴⁴ ACQ-5 results tended to show a low level of controlled asthmatics patients. Nevertheless, further studies are needed in monosensitized or polysensitized population to confirm these results, particularly using molecular diagnosis. Sensitization to perennial allergens was associated with more extensive diagnostic tests use both for rhinitis and for asthma. However, use of antihistamines and topical nasal steroids in rhinitis, and use of immunotherapy in asthma, were more common for seasonal allergens.

The results obtained in this study indicate that, despite modern treatments, not all patients can achieve full control of asthma symptoms. Therefore, it can be suspected that poorer symptom control adversely affects asthma patients' HRQoL, and patients exhibiting better symptom control have higher QoL scores. It seems that in our patients, the degree of control (medical view of the disease) coincides in part with the degree of HRQoL (patient's view).

In our study, quality of life related to rhinitis is more affected in patients diagnosed with rhinitis and asthma than in those who only have nasal symptoms. This observation could be based on the common mechanisms of allergic inflammation in both respiratory diseases³² and confirm that in patients diagnosed with allergic respiratory disease the involvement of the upper and lower airways should always be considered.

We have not shown differences in the effect on HRQoL between patients (whether rhinitis sufferers or both rhinitis and asthma sufferers) sensitive to seasonal and perennial allergens taken as global groups (Table 4), or between perennial allergens individually considered (Table 5). Such findings can probably be related to different environmental allergen levels: patients sensitized to perennial allergens or seasonal allergens with a prolonged presence in the environment are symptomatic during all the year: thus symptoms are more tolerable and perception of symptoms is reduced compared to patients allergic to pollens, who suffer a sudden and limited exposure.⁴⁵ However, sudden and intense exposure to allergens such as *Olea* pollens induces a greater sense of discomfort. In this respect, Bousquet et al¹⁷ showed that the severity of the disease had more effect than its duration. This is consistent with the data observed in our study.

Our study had some limitations. Design was not assessor-blinded, but this is logistically unavoidable in an observational study including more than 300 centers. Importantly, multiple endpoints were analyzed and no adjustment was used. However, this is a reasonable approach due to the exploratory and hypothesis-generating nature of the present study.

Both sensitization and clinical development of allergic disease are complex processes that depend at least in part, of the allergen.³⁴ Different types of aeroallergens (seasonal vs perennial) and specific sensitization profiles are associated with different allergic respiratory clinical pictures (rhinitis with/without asthma), different clinical symptoms and severity. This is a new, mostly unexplored field that could have remarkable implications to predict later clinical course in sensitized individuals and to select appropriate management approaches based on allergen prevalence profiles in specific geographical areas. Further studies are warranted.

Acknowledgement

Statistical analyses assistance was provided by Laura Corredoira; BioClever, Barcelona, Spain.

Editorial assistance was provided by Content Ed Net, Madrid, Spain.

Authors' contribution

All authors contributed to the study design, development, analysis and writing the manuscript.

Conflicts of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

References

1. Spergel JM. From atopic dermatitis to asthma: the atopic march. *Ann Allergy Asthma Immunol* 2010;105:99–106; quiz 107–9, 117.
2. Holgate ST, Polosa R. Treatment strategies for allergy and asthma. *Nat Rev Immunol* 2008;8:218–30.
3. von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy*

- 1998;28 Suppl 5:45–9; discussion 50–1.
4. Settipane RA, Charnock DR. Epidemiology of rhinitis: allergic and nonallergic. *Clin Allergy Immunol* 2007;19:23–34.
 5. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004;24:758–64.
 6. The European Community Respiratory Health Survey II. *Eur Respir J* 2002;20:1071–9.
 7. Alergológica 2005. Factores epidemiológicos, clínicos y socioeconómicos de las enfermedades alérgicas en España en 2005. Madrid: Sociedad Española de Alergia e Inmunología Clínica y Schering-Plough; 2006.
 8. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63 Suppl 8:8–160.
 9. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466–76.
 10. GEMA 2009 (Spanish guideline on the management of asthma). *J Investig Allergol Clin Immunol* 2010;20 Suppl 1:1–59.
 11. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;111:1171–83; quiz 1184.
 12. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000;106:S201–5.
 13. Navarro A, Colás C, Antón E, Conde J, Dávila I, Dordal MT, et al. Epidemiology of allergic rhinitis in allergy consultations in Spain: Alergológica-2005. *J Investig Allergol Clin Immunol* 2009;19 Suppl 2:7–13.
 14. Navarro A, Valero A, Juliá B, Quirce S. Coexistence of asthma and allergic rhinitis in adult patients attending allergy clinics: ONEAIR study. *J Investig Allergol Clin Immunol* 2008;18:233–8.
 15. Sunyer J, Jarvis D, Pekkanen J, Chinn S, Janson C, Leynaert B, et al. Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. *J Allergy Clin Immunol* 2004;114:1033–9.
 16. Bousquet P-J, Leynaert B, Neukirch F, Sunyer J, Janson CM, Anto J, et al. Geographical distribution of atopic rhinitis in the European Community Respiratory Health Survey I*. *Allergy* 2008;63:1301–9.
 17. Bousquet P-J, Chinn S, Janson C, Kogevinas M, Burney P, Jarvis D. Geographical variation in the prevalence of positive skin tests to environmental aeroallergens in the European Community Respiratory Health Survey I. *Allergy* 2007;62:301–9.
 18. Moral L, Roig M, Garde J, Alós A, Toral T, Fuentes MJ. Allergen sensitization in children with asthma and rhinitis: marked variations related to age and microgeographical factors. *Allergol Immunopathol (Madr)* 36:128–33.
 19. Li J, Huang Y, Lin X, Zhao D, Tan G, Wu J, et al. Influence of degree of specific allergic sensitivity on severity of rhinitis and asthma in Chinese allergic patients. *Respir Res* 2011;12:95.
 20. Delgado J, Dávila ID, Domínguez-Ortega J, Quirce S, Martí-Guadano E, Valero A. Quality of life in patients with respiratory allergy is influenced by the causative allergen. *J Investig Allergol Clin Immunol* 2013;23:309–14.
 21. Domínguez-Ortega J, Quirce S, Delgado J, Dávila I, Martí-Guadano E, Valero A. Diagnostic and therapeutic approaches in respiratory allergy are different depending on the profile of aeroallergen sensitisation. *Allergol Immunopathol (Madr)* 42:11–8.

22. Miguères M, Dávila I, Frati F, Azpeitia A, Jeanpetit Y, Lhéritier-Barrand M et al. Types of sensitization to aeroallergens: definitions, prevalences and impact on the diagnosis and treatment of allergic respiratory disease. *Clin Transl Allergy* 2014; 4:16.
23. Valero A, Ferrer M, Sastre J, Navarro AM, Monclús L, Martí-Guadaño E, et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the Allergic Rhinitis and its Impact on Asthma severity items. *J Allergy Clin Immunol* 2007;120:359–65.
24. Juniper EF, O’Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–7.
25. Valero A, Alonso J, Antepara I, Baró E, Colas C, del Cuvillo A, et al. Development and validation of a new Spanish instrument to measure health-related quality of life in patients with allergic rhinitis: the ESPRINT questionnaire. *Value Health* 10:466–77.
26. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14:32–8.
27. Sanjuàns C, Alonso J, Sanchís J, Casan P, Broquetas JM, Ferrie PJ, et al. [The quality-of-life questionnaire with asthma patients: the Spanish version of the Asthma Quality of Life Questionnaire]. *Arch Bronconeumol* 1995;31:219–26.
28. Nyembue TD, Ntumba W, Omadjela LA, Muyunga C, Hellings PW, Jorissen M. Sensitization rate and clinical profile of Congolese patients with rhinitis. *Allergy Rhinol (Providence)* 2012;3:e16–24.
29. Sánchez-Caraballo J, Diez-Zuluaga S, Cardona-Villa R. [Sensitization to aeroallergens in allergic patients from Medellín, Colombia]. *Rev Alerg Mex* 59:139–47.
30. Ozkaya E, Sogut A, Küçükkoç M, Eres M, Acemoglu H, Yuksel H, et al. Sensitization pattern of inhalant allergens in children with asthma who are living different altitudes in Turkey. *Int J Biometeorol* 2015;
31. Toppila-Salmi S, Huhtala H, Karjalainen J, Renkonen R, Mäkelä MJ, Wang DY, et al. Sensitization pattern affects the asthma risk in Finnish adult population. *Allergy* 2015;70:1112–20.
32. Olivieri M, Heinrich J, Schlünssen V, Antó JM, Forsberg B, Janson C et al. The risk of respiratory symptoms on allergen exposure increases with increasing specific IgE levels. *Allergy* 2016;71:859-68.
33. Kelly LA, Erwin EA, Platts-Mills TAE. The indoor air and asthma: the role of cat allergens. *Current Opinion in Pulmonary Medicine*. 2012;1:29–34
34. Schoos AM, Chawes BL, Jelding-Dannemand E, Elfman LB, Bisgaard H. Early indoor aeroallergen exposure is not associated with development of sensitization or allergic rhinitis in high-risk children. *Allergy* 2016;71:684-91
35. Bielory L. Allergic conjunctivitis and the impact of allergic rhinitis. *Curr Allergy Asthma Rep* 2010;10:122–34.
36. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. *Allergy* 2005;60:350–3.
37. Pereira C, Valero A, Loureiro C, Dávila I, Martinez-Cócerca C, Murio C, et al. Iberian study of aeroallergens sensitisation in allergic rhinitis. *Eur Ann Allergy Clin Immunol* 2006;38:186–94.
38. Milani M, Pecora S; Rainbow Study Investigator Group. Clinical relevance of non-grass pollens respiratory allergies in Italy and effects of specific sublingual immunotherapy: The Rainbow Trial, a multicenter 3-year prospective observational study. *Eur Ann Allergy Clin Immunol* 2011; 43: 111-6.

39. Olaguibel JM, Quirce S, Juliá B, Fernández C, Fortuna AM, Molina J, et al. Measurement of asthma control according to Global Initiative for Asthma guidelines: a comparison with the Asthma Control Questionnaire. *Respir Res* 2012;13:50.
40. Hayes D Jr, Jhaveri MA, Mannino DM, Strawbridge H, Temprano J. The effect of mold sensitization and humidity upon allergic asthma. *Clin Respir J* 2013; 7: 135-44.
41. Serrano-Pariente J, Rodrigo G, Fiz JA, Crespo A, Plaza V, High Risk Asthma Research Group. Identification and characterization of near-fatal asthma phenotypes by cluster analysis. *Allergy* 2015; 70: 1139-47.A
42. Domínguez Ortega J, Martín Santos S, Hinojosa Mena-Bernal J, Alonso Llamazares A, Llamas C, Plaza A, et al. Analysis of 83 bronchospasm episodes seen at urgent care during one spring night. *Allergol Immunopathol (Madr)* 2001; 29: 197-20.
43. Brito FF, Gimeno PM, Carnes J, Marin R, Fernandez-Caldas E, Lara P, et al. Olea europea pollen counts and aeroallergen levels predict clinical symptoms in patients allergic to olive pollen. *Ann Allergy Asthma Immunol* 2011; 106: 146-52.
44. Quirce S. Asthma in Alergologica 2005. *J Investig Allergol Clin Immunol* 2009; 19: 14-20.
45. Bousquet J, Neukirch F, Bousquet PJ, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol* 2006; 17:158–162.

Table 1. Demographic data and baseline characteristics for the whole population

Characteristics	
Evaluated patients, n	2507
Age, years, mean±SD	35.0±11.3
Sex	
Women, n (%)	1347 (54.0%)
Men, n (%)	1148 (46.0%)
Body mass index, mean±SD	24.58±4.02
Smoking	
Never smoker, n (%)	1779 (71.2%)
Former smoker, n (%)	292 (11.7%)
Current smoker, n (%)	426 (17.1%)
Place of residence	
Rural (<2500 residents), n (%)	190 (7.6%)
Half-urban (2500 to 15000 residents), n (%)	479 (19.2%)
Urban (>15000 resident), n (%)	1825 (73.2%)
Geographical zone	
Coastal, n (%)	767 (30.8%)
Inland, n (%)	1722 (69.2%)
Referral from	
Primary care, n (%)	1003 (86.9%)
Specialists, n (%)	151 (13.1%)
Family history (first degree) of atopia, n (%)	1172 (48.6%)
Concurrent allergic diseases	
Conjunctivitis, n (%)	1787 (73.8%)
Atopic dermatitis, n (%)	272 (12.0%)
Food allergy, n (%)	242 (10.6%)
Drug allergy, n (%)	152 (6.7%)
Allergy to hymenoptera, n (%)	15 (0.7%)

Table 2. Baseline characteristics for the whole population

Clinical characteristics	
Allergic disorder	
Rhinitis, %	59%
Rhinitis and asthma, %	38%
Asthma, %	3%
Duration of rhinitis (years), mean±SD	7.3±7.7
Duration of asthma (years), mean±SD	6.2±7.9
Time to asthma development since rhinitis onset (years), mean±SD	2.3±4.2
Severity of rhinitis	
Mild, %	16%
Moderate, %	70%
Severe, %	14%
Type of rhinitis	
Intermittent, %	34%
Persistent, %	66%
ARIA items	
Disturbing symptoms, %	87%
Daily activities, sport, leisure, %	51%
School/work performance, %	41%
Sleep disorder, %	47%
Severity of asthma	
Intermittent, %	28%
Mild persistent, %	32%
Moderate persistent, %	38%
Severe persistent, %	2%
Asthma control	
Controlled, %	40%
Partially controlled, %	47%
Uncontrolled, %	13%

Table 3. Quality of life and control for the whole population.

Scale	mean±SD	p-value
Quality of life, rhinitis ESPRINT-15	2.41±1.31	
Quality of life, rhinitis ESPRINT-15 by allergic disorder		
Rhinitis	2.36±1.29	p=0.018
Rhinitis and asthma	2.48±1.33	
Quality of life asthma Mini-AQLQ	4.96±1.23	
Quality of life asthma Mini-AQLQ by asthma control (based on current guidelines criteria)		
Controlled	5.64±1.11	p<0.001
Partially controlled	4.66±1.01	
Uncontrolled	4.0±1.20	
Asthma control ACQ-5	1.63±1.20	
ACQ-5 by asthma control (based on current guidelines criteria)		
Controlled	0.85±0.89	p<0.001
Partially controlled	1.96±1.00	
Uncontrolled	2.83±1.15	
ACQ-5 by asthma control score		
Controlled	29%	
Partially controlled	22%	
Uncontrolled	50%	

Table 4. Clinical characteristics and quality of life in patients allergic to perennial versus seasonal allergens

	Perennial allergens (n=791)	Seasonal allergens (n=973)	P-value
Allergic disorder			
Rhinitis, n (%)	415 (52.5%)	673 (69.2%)	<0.0001
Rhinitis and asthma, n (%)	333 (42.1%)	284 (29.2%)	
Asthma, n (%)	43 (5.4%)	16 (1.6%)	
Duration of rhinitis (years), mean±SD	7.4±7.7	6.8±7.7	0.2574
Duration of asthma (years), mean±SD	6.6±8.0	5.7±7.9	0.2478
Time to asthma development since rhinitis onset (years), mean±SD	1.7±3.9	2.8±4.3	0.0003
Severity of rhinitis			
Mild, n (%)	148 (20.2%)	127 (13.5%)	0.0008
Moderate, n (%)	483 (66.0%)	686 (73.0%)	
Severe, n (%)	101 (13.8%)	127 (13.5%)	
Type of rhinitis			
Intermittent, n (%)	229 (30.8%)	358 (37.7%)	0.0031
Persistent, n (%)	514 (69.2%)	591 (62.3%)	
ARIA items			
Disturbing symptoms, n (%)	626 (84.7%)	843 (88.8%)	0.0124
Daily activities, sport, leisure, n (%)	321 (44.2%)	501 (53.5%)	0.0001
Sleep disorder, n (%)	318 (43.3%)	439 (47.0%)	0.1342
School/work performance, n (%)	248 (34.3%)	403 (43.4%)	0.0002
Severity of asthma			
Intermittent, n (%)	96 (25.9%)	91 (30.7%)	0.0243
Mild persistent, n (%)	107 (28.9%)	102 (34.5%)	
Moderate persistent, n (%)	155 (41.9%)	100 (33.8%)	
Severe persistent, n (%)	12 (3.2%)	3 (1.0%)	
Asthma control			
Controlled, n (%)	147 (39.8%)	122 (41.4%)	0.6772
Partially controlled, n (%)	167 (45.3%)	136 (46.1%)	
Uncontrolled, n (%)	55 (14.9%)	37 (12.5%)	
Concurrent allergic diseases			
Conjunctivitis, n (%)	462 (60.6%)	740 (78.6%)	<0.0001
Atopic dermatitis, n (%)	88 (12.2%)	95 (10.7%)	0.3592
Food allergy, n (%)	59 (8.1%)	99 (11.1%)	0.0488
Drug allergy, n (%)	63 (8.8%)	44 (5.0%)	0.0026
Allergy to hymenoptera, n (%)	8 (1.1%)	2 (0.2%)	0.0500
Quality of life, rhinitis ESPRINT-15, mean±SD	2.28±1.30	2.38±1.31	0.1302
Quality of life asthma Mini-AQLQ, mean±SD	4.94±1.25	5.08±1.21	0.1842
Asthma control ACQ-5, mean±SD	1.63±1.24	1.54±1.16	0.4961

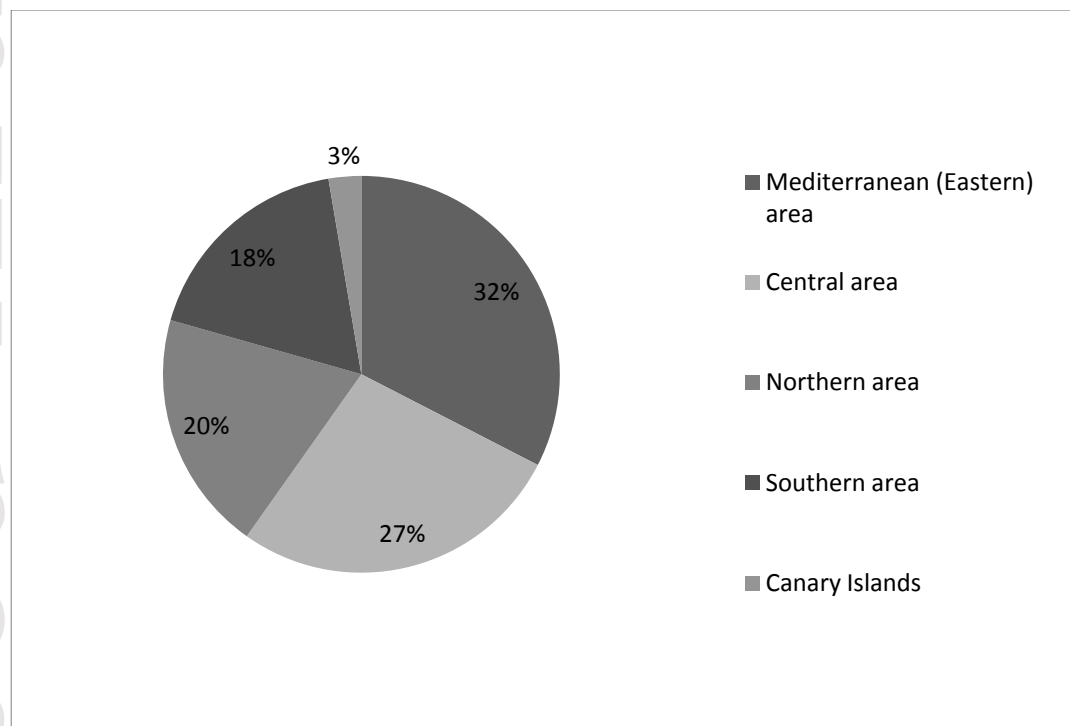
Table 5. Clinical characteristics and quality of life in patients allergic to different allergens: perennial (only those achieving statistical significance are shown)

	<i>Alternaria</i> (n=140)	Cat/dog dander (n=299)	HDM (n=352)	P-value
Allergic disorder				
Rhinitis, n (%)	54 (38.6%)	145 (48.5%)	216 (61.4%)	<0.0001
Rhinitis and asthma, n (%)	69 (49.3%)	141 (47.2%)	123 (34.9%)	
Asthma, n (%)	17 (12.1%)	13 (4.3%)	13 (3.7%)	
Duration of rhinitis (years), mean±SD	9.5 ± 9.1	6.9 ± 7.5	7.0 ± 6.9	0.0490
Duration of asthma (years), mean±SD	9.1 ± 9.4	5.5 ± 7.3	6.0 ± 7.1	0.0282
Severity of rhinitis				
Mild, n (%)	15 (12.4%)	67 (23.9%)	66 (19.9%)	0.0674
Moderate, n (%)	87 (71.9%)	171 (61.1%)	225 (68.0%)	
Severe, n (%)	19 (15.7%)	42 (15.0%)	40 (12.1%)	
Type of rhinitis				
Intermittent, n (%)	30 (24.8%)	103 (36.3%)	96 (28.4%)	0.0311
Persistent, n (%)	91 (75.2%)	181 (63.7%)	242 (71.6%)	
Severity of asthma				
Intermittent, n (%)	16 (19.0%)	38 (25.0%)	42 (31.3%)	0.0291
Mild persistent, n (%)	30 (35.7%)	33 (21.7%)	44 (32.8%)	
Moderate persistent, n (%)	35 (41.7%)	77 (50.7%)	43 (32.1%)	
Severe persistent, n (%)	3 (3.6%)	4 (2.6%)	5 (3.7%)	
Asthma control				
Controlled, n (%)	25 (29.8%)	60 (39.7%)	62 (46.3%)	0.0287
Partially controlled, n (%)	49 (58.3%)	62 (41.1%)	56 (41.8%)	
Uncontrolled, n (%)	10 (11.9%)	29 (19.2%)	16 (11.9%)	
Concurrent allergic diseases				
Conjunctivitis, n (%)	75 (57.3%)	193 (66.3%)	194 (57.1%)	0.0409
Quality of life, rhinitis ESPRINT-15, mean±SD	2.25 ± 1.29	2.29 ± 1.31	2.29 ± 1.30	0.9678
Quality of life asthma Mini-AQLQ, mean±SD	5.08 ± 1.15	4.91 ± 1.33	4.87 ± 1.22	0.4864
Asthma control ACQ-5, mean±SD	1.53 ± 1.15	1.73 ± 1.31	1.58 ± 1.23	0.5625

Table 6. Clinical characteristics and quality of life in patients sensitized to different allergens: seasonal (only those achieving statistical significance are shown)

	Cypress (n=204)	Grass (n=322)	Grass + Olive (n=348)	Olive (n=93)	<i>Parietaria</i> (n=215)	Plane tree (n=139)	P-value
Allergic disorder							
Rhinitis, n (%)	153 (75.0%)	214 (66.5%)	187 (53.7%)	62 (66.7%)	152 (70.7%)	92 (66.2%)	0.0001
Rhinitis and asthma, n (%)	47 (23.0%)	105 (32.6%)	150 (43.1%)	29 (31.2%)	60 (27.9%)	43 (30.9%)	
Asthma, n (%)	4 (2.0%)	3 (0.9%)	11 (3.2%)	2 (2.2%)	3 (1.4%)	4 (2.9%)	
Duration of rhinitis (years), mean (SD)	6.5 (7.6)	6.7 (7.6)	7.7 (7.7)	5.9 (7.2)	7.6 (8.1)	6.8 (7.3)	0.0151
Duration of asthma (years), mean (SD)	5.4 (9.1)	4.5 (4.7)	5.5 (7.0)	2.8 (3.8)	7.5 (9.8)	8.0 (9.5)	0.0105
Type of rhinitis							
Intermittent, n (%)	82 (41.2%)	126 (39.7%)	103 (30.9%)	27 (30.7%)	61 (28.9%)	62 (46.3%)	0.0014
Persistent, n (%)	117 (58.8%)	191 (60.3%)	230 (69.1%)	61 (69.3%)	150 (71.1%)	72 (53.7%)	
Quality of life, rhinitis ESPRINT-15, mean (SD)	2.24 (1.35)	2.43 (1.25)	2.72 (1.28)	2.86 (1.26)	2.33 (1.29)	2.20 (1.37)	<0.0001
Quality of life asthma Mini-AQLQ, mean (SD)	5.00 (0.90)	5.26 (1.22)	4.70 (1.21)	4.37 (1.20)	5.29 (1.19)	4.96 (1.35)	0.0001
Asthma control ACQ-5, mean (SD)	1.53 (1.01)	1.41 (1.14)	1.92 (1.22)	2.23 (1.22)	1.32 (1.07)	1.68 (1.26)	0.0003

Figure 1. Geographical distribution in participating centers (n = 301)



Geographical area	Number	%
Mediterranean (Eastern)	98	32.6%
Central	82	27.2%
Northern	59	19.6%
Southern	54	17.9%
Canary Islands	8	2.7%

Figure 2. Sensitization to relevant allergens in patients with rhinitis with/without asthma ($p<0.0001$).

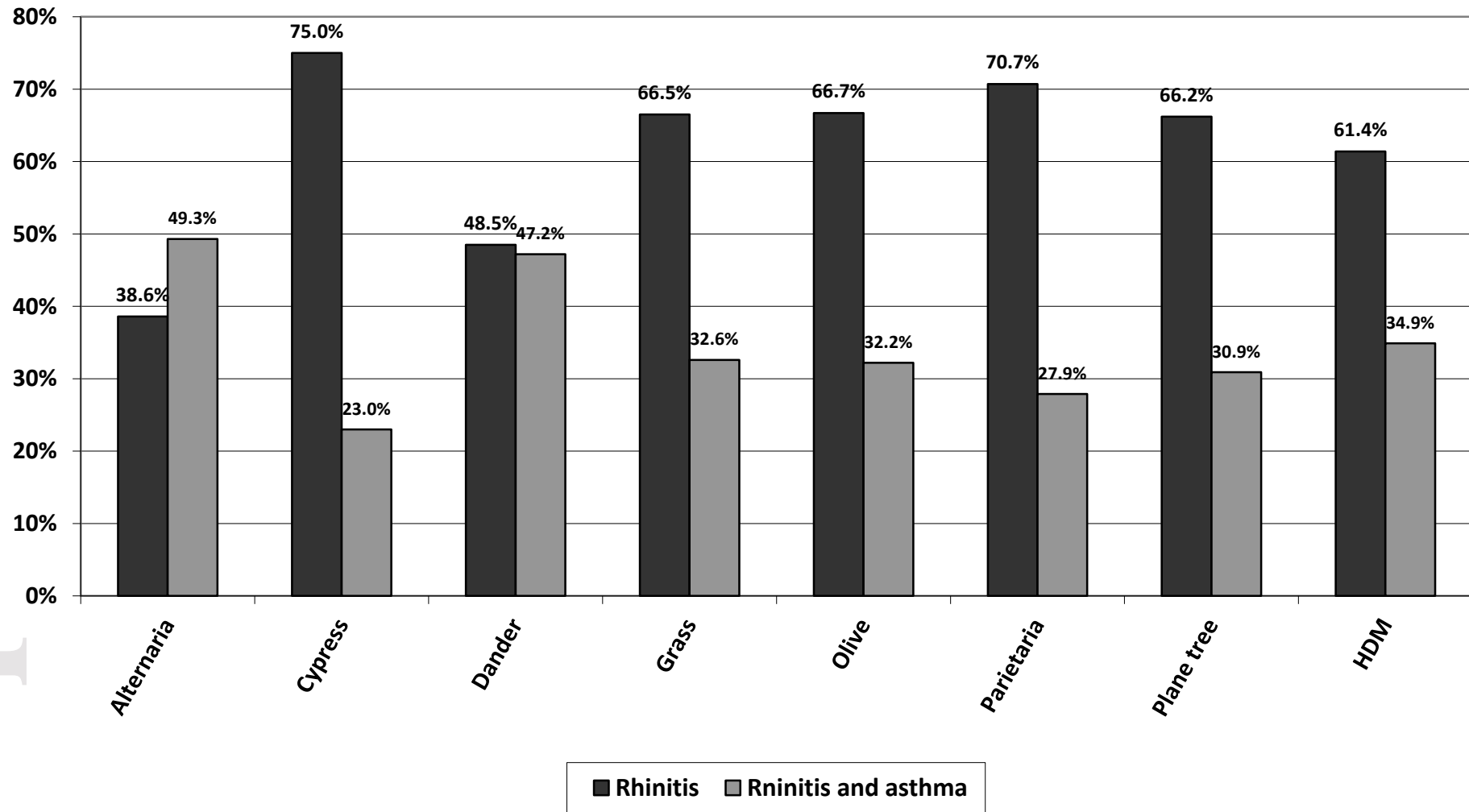


Figure 3. Logistic regression model: perennial and seasonal allergens (reference category: perennial allergens)

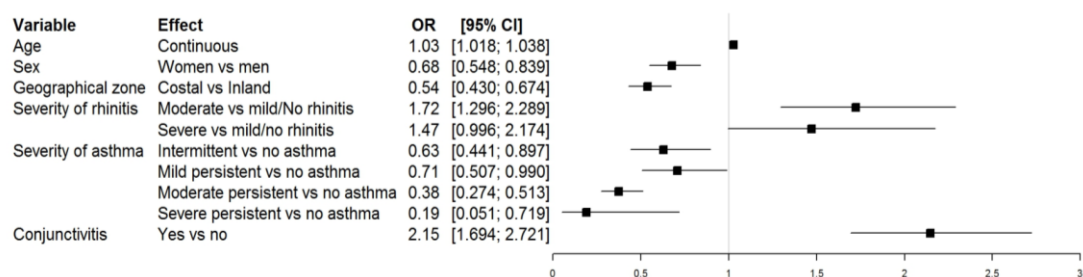


Figure 4. Multinomial logistic regression model for perennial allergens: *Alternaria* vs. dander vs. HDM (Reference category: *Alternaria*)

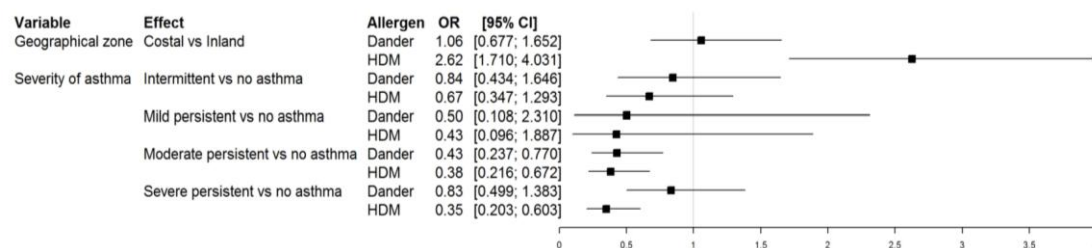


Figure 5. Multinomial logistic regression model for seasonal allergens: cypress vs grass vs grass plus olive vs olive vs *Parietaria* vs plane tree (Reference category: cypress).

