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ORIGINAL ARTICLE

Temporal relationship of allergic rhinitis with asthma and other co-morbidities in a Mediterranean country: A retrospective study in a tertiary reference allergy clinic

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Abstract
Background: Allergic rhinitis is a global health problem which causes major illness and represents a risk factor for asthma. The primary aim of the study was to record the clinical pattern of allergic rhinitis and its temporal relation with asthma in a Greek population.
Methods: Three-hundred and sixteen subjects with documented diagnosis of allergic rhinitis in a two-year period were included in this study. All participants completed a standardised questionnaire with full retrospective epidemiological data for rhinitis; in addition, serum IgE measurement and skin prick tests with 22 common inhalant allergens were carried out, while spirometry was performed in subjects with self-reported or doctor-diagnosed asthma. All subjects with at least one positive skin test were included in study analysis.
Results: One-hundred and sixty five out of 316 patients (49.1%) stated self reported-asthma while in 63/316 (19.9%) asthma was documented with spirometry. One hundred out of 165 (60.6%) had rhinitis as first clinical manifestation while in 24/165 (14.5%) asthma symptoms appeared first; the remaining 31/165 (24.9%) reported simultaneous onset of upper and lower airways' symptoms. About 68.5% were sensitised to seasonal allergens exclusively, while 50% were sensitised to ≥ 1 of *Parietaria*, grasses sp., *Olea eur.* The duration of rhinitis in the subpopulation of patients with self-reported asthma ($n=165$) was significantly higher compared with non-asthmatics (mean=3.22 years, $p<0.001$). Survival analysis for the estimation of asthma onset showed that the mean time interval with rhinitis only is 16.6 years (median 12 years, incidence 0.0596).
Conclusions: The unique environmental conditions and the aerobiology of each area clearly affect the clinical features of respiratory allergy.

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Introduction

Allergic rhinitis is a global health problem which causes major illness and disability worldwide and according to rather conservative estimates, it occurs in over 500 million people around the world[1]. Large epidemiological studies have demonstrated a large variation in the prevalence of rhinitis symptoms throughout the world[2]. The International Study on Asthma and Allergy in Childhood Phase (ISAAC) I reported that the prevalence of rhinitis with itchy-watery eyes (rhinoconjunctivitis) over the past year varied between centres from 0.8% to 14.9% in 6–7-year olds and from 1.4% to 39.7% in 13–14-year olds. In ISAAC III[3], it was found that in the 6–7-year age group, there is a global increase in rhinitis prevalence across most countries. In the 13- to 14-year age group, there is also a global increase in allergic rhinitis in countries where low, medium and high prevalence rates were found during ISAAC Phase I. On the other hand, rates are levelling off or decreasing in countries with high prevalence. It is likely that environmental factors were responsible for the major differences between countries.

The clinical definition of rhinitis is difficult to use in epidemiological studies as it is rather impossible to obtain laboratory evidence of the underlying immune mechanism; so the use of questionnaires as the only diagnostic tool leads to an overestimation of allergic rhinitis. The attributable fraction of documented IgE sensitisation in patients with diagnosis of allergic rhinitis by questionnaires is almost 50%[4].

According to numerous epidemiological and clinical studies, rhinitis and asthma often co-exist and share common risk factors, including atopy as the most important, and might even be manifestations of the same disease[5]. The few longitudinal studies that have addressed the temporal relation between rhinitis and asthma in respiratory allergy report that rhinitis precedes the development of asthma in most cases, suggesting that it represents a risk factor for asthma[6,7]. However, comparison of the results of these studies is difficult mainly due to methodological reasons as they did not use standardised methods for the diagnosis of asthma and rhinitis.

Due to the clear differences in the features of allergic rhinitis between different populations and considering the lack of relevant data referring to the geographical area of Greece, we have conducted this study with the primary aim to record the clinical pattern of allergic rhinitis and its temporal relation with asthma in a Greek population. Secondly, the record of co-morbidities and the investigation of possible risk factors such as sex, age, pattern of sensitisation, smoking habit, allergic conjunctivitis, exercise-induced asthma and sinusitis, for asthma in subjects with allergic rhinitis in our area were additional goals of our study.

Patients and methods

Patients' characteristics—study design

All patients referred to the Outpatient Clinic of the Allergy Unit of 'Attikon' University Hospital with documented diagnosis of allergic rhinitis, from April 2006 until April 2008 were included in this study. Inclusion criteria of the study were: (a) documented diagnosis of allergic rhinitis; (b) age $\geq$12 years; and (c) non-visible nasal polyps in anterior rhinoscopy. The diagnosis of allergic rhinitis was based on the typical clinical symptoms and the documentation of sensitisation with skin prick tests (SPTs), to at least one inhalant allergen according to the recently published ARIA document[1].

The records of the present and past medical history of certain parameters (the reply options are presented in brackets) were obtained from each subject referred for rhinitis: (a) age (in years); (b) sex (male, female); (c) smoking habit (smoker, non-smoker, ex-smoker); (d) duration of rhinitis symptoms (years); (e) type of rhinitis (seasonal, perennial, perennial with seasonal exacerbation); (f) self-reported symptoms of asthma (yes, no); (g) past or present documented diagnosis of asthma—symptoms suggestive of asthma as in self-reported asthma combined with obstructive spirometric values—(yes, no) according to GINA guidelines[8]; (h) symptoms of exercise induced asthma (yes, no); (i) duration of symptoms of asthma (years); (j) allergic conjunctivitis (yes, no); (k) history of chronic sinusitis (yes, no); (l) familiar history of atopic diseases; rhinitis, asthma, atopic dermatitis and/or food allergy in either of the parents (yes, no); (m) history of gastrooesophageal reflux (yes, no); (n) total serum IgE (IU/ml); (o) pattern of sensitisation (monosensitisation, polysensitisation when more than one allergen); (p) type of allergens (seasonal, perennial or both); (q) specific allergens; and (r) past or present history of concomitant atopic disorders (none, atopic dermatitis, food allergy, both, oral allergy syndrome).

The diagnostic criteria for allergic rhinitis were two or more of the following symptoms for $>$1 h on most days (a. watery rhinorrhea, b. sneezing, c. nasal obstruction, d. nasal pruritus) with documented IgE-sensitisation to at least one inhalant allergen. The patient-reported asthma was assessed with positive reply to at least one of five questions (a. did you have an attack or recurrent attacks of wheezing?, b. do you have a troublesome cough at night?, c. do you experience wheezing, chest tightness, or cough after exposure to airborne allergens or pollutants?, d. do your colds "go to the chest" or take more than 10 days to clear up?, e. Are symptoms improved by appropriate asthma treatment?)[8].

Subjects attended the Allergy Clinic on two occasions, 1–2 months apart. During the first visit, all subjects completed the standardised questionnaire, a blood sample was taken for determination of serum IgE concentration in IU/ml, (UniCAP system, Phadia, Uppsala, Sweden) and then an allergist obtained a full medical history and performed physical examination. Arterior rhinoscopy was performed in all subjects. In addition, the consulting allergist provided explanations to any possible query about the questionnaire. At the second visit, SPTs were carried out in all subjects and spirometry was performed in subjects with self-reported or doctor-diagnosed asthma.

All subjects with at least one positive skin test were included in study analysis.

Skin prick tests

Atopy was assessed in all participants by SPTs, using a battery of 22 common inhalant allergens: *Dermatophagoides pteronyssinus, Dermatophagoides farinae, Phleum pr,*

Cynodon D, Lolium per, Secale cer, Parietaria off, Artemisia vul, Taraxacum Vulg, Plantago lan, Olea Europea, Platanus, Betula, Quercus, Fagus, Poplar, Cat dander, Dog epithelium, Cladosporium, Penicillium, *Alternaria Alt*, Aspergillus mix; positive (histamine hydrochloride 10 mg/dl) and negative control (normal saline) were also used (Stallergenes, Paris,

Table 1 Descriptive characteristics of study population.

	Number of patients	Frequency
a: categorical variables		
Sex		
Male	182	57.6
Female	134	42.4
Smoking habit		
No	243	78.1
Yes	60	19.3
Ex-smoker	8	2.6
Type of rhinitis		
Seasonal	212	67.1
Perennial	40	12.7
Perennial with seasonal exacerbation	64	20.3
Self-reported asthma		
no	161	50.9
yes	155	49.1
Documented asthma		
no	253	80.1
yes	63	19.9
Exercise-induced asthma		
no	290	91.8
yes	26	8.2
Gastrointestinal reflux		
no	315	99.7
yes	1	0.3
Chronic rhinosinusitis		
no	280	88.6
yes	36	11.4
Familiar history of atopic disease		
yes	245	77.5
no	71	22.5
Allergic conjunctivitis		
no	152	48.1
yes	164	51.9
Sensitisation pattern		
monosensitisation	111	35.2
polysensitisation	204	64.8
Type of allergens		
Seasonal	212	67.3
Perennial	25	7.9
Seasonal+perennial	78	24.8
History of atopic disorders		
No	284	90.4
Atopic dermatitis	11	3.5
Food allergy	9	2.9
Oral allergy syndrome	10	3.2

	Rhinitis ($n=161$) Mean±SD	**Rhinitis+asthma ($n=155$)** Mean±SD	**Statistical significance** *p* value
b: numeric variables			
Age (years)	28.32±11.25	36.13±13.28	0.01
IgE (IU/ml)	421±824.19	390±904.78	NS
Rhinitis duration (years)	8.83±7.30	12.05±8.58	0.03
Asthma duration (years)	–	7.35±7.28	–

France). A wheal diameter >3 mm was considered as criterion of positive SPT.

Positive SPTs in more than one species of grasses were considered as monosensitisation due to the well-documented extended cross-reactivity.

Spirometry

A MasterScope spirometer (Erich Jaeger, Wurzburg, Germany) was used for flow volume spirometry. The best of three manoeuvres was expressed as a percentage of the predicted value.

Statistical analysis

Data of continuous variables are presented as mean and standard deviation (SD). Normality of distribution was examined with Kolmogorov-Smirnov and Shapiro-Wilk's test. In cases with a normal distribution, paired or independent t-test were used for analysis of differences of means. In the case of a non-normally distributed variable, a Mann-Whitney U test was carried out.

Chi-square test and Fischer exact test were used to analyse differences in categorical variables (sex, type of sensitisation, etc.). In all cases in which the main outcome variable was the time interval to the occurrence of asthma, the data was firstly graphically displayed by using the Kaplan-Meier estimator for plotting the survival functions, and survival curves were compared using a log-rank test.

A two tailed p-value less than 0.05 was considered to indicate statistical significance. All analyses were performed with the Statistical Package for Social Science (SPSS, Chicago, IL, USA), version 13.0.

Results

Descriptive characteristics of study population

Three-hundred and sixteen subjects who fulfilled the inclusion criteria were included in study analysis. The descriptive characteristics of study population are presented in Table 1. One-hundred and sixty five out of 316 patients (49.1%) stated self-reported asthma, while in 63/316 (19.9%) asthma was documented with lung function tests. All but one (62/63) subjects with doctor-diagnosed asthma also stated self-reported asthma ($p<0.001$). One hundred out of 165 (60.6%) patients with self-reported asthma, reported rhinitis as the first clinical manifestation while in 24/165 (14.5%) asthma symptoms appeared first; the remaining 31/165 (24.9%) reported simultaneous onset of symptoms from upper and lower airways.

The prevalence of the sensitising allergens in our population is presented in Figure 1. In our population, 68.5% were sensitised to seasonal allergens exclusively, while 50% proved to be sensitised in one of the three prevalent allergens in our country (*Parietaria, grasses* sp., *Olea eur.*)

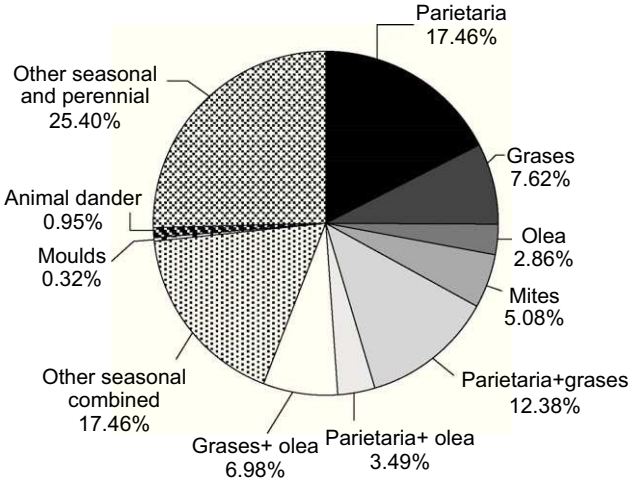

Figure 1 Prevalence of sensitisation in study population.

Correlation analysis

In the whole population

The duration of rhinitis in the subpopulation of patients with self-reported asthma ($n=165$) was significantly higher compared with non-asthmatics (mean=3.22 years, $p<0.001$). Similarly, the subgroup with documented asthma ($n=65$) also had increased duration of rhinitis (mean=2.04 years, $p<0.032$).

Linear regression analysis for the estimation of possible factors that affect the duration of rhinitis, presented in Table 2, showed that: (i) for every additional year of age the duration of rhinitis increased 0.31 years; (ii) patients with self-reported asthma have almost 3.5 years longer duration of rhinitis; (iii) current smoking is associated with longer duration (mean =1.93 years vs. non-smokers); (iv) perennial rhinitis with seasonal exacerbation had a duration on average 2.16 years longer compared with seasonal rhinitis; and (v) polysensitisation was associated with 2.5 years longer duration of rhinitis in comparison with monosensitisation.

A multinomial logistic regression model was used to investigate the factors that affect the pattern of allergic rhinitis (Table 3). It was found that concomitant allergic conjunctivitis increases almost threefold (odds ratio 3.34) the possibility of seasonal vs. perennial rhinitis. By contrast, chronic sinusitis favours the existence of perennial rhinitis vs. seasonal almost sixfold (odds ratio 5.96) and perennial with seasonal exacerbation vs. seasonal almost 2.5 times (odds ratio 2.64).

Linear regression analysis for chronic sinusitis showed that the probability of developing disease depends on the pattern of rhinitis. Patients with perennial rhinitis have 5 times increased possibility of sinusitis compared with seasonal rhinitis and 2.5 times compared to perennial with seasonal exacerbation, respectively.

In subpopulation with asthma

Statistical analysis showed that self-reported asthma as well as documented asthma did not associate with sex, age, pattern of sensitisation, smoking habit, allergic conjunctivitis

Table 2 Linear regression model for rhinitis duration.

Model	Coefficients[a]						
	Unstandardised Coefficients		Standardised Coefficients			95.0% Confidence interval for B	
	B	Std. error	Beta	t	Sig.	Lower bound	Upper bound
(Constant)	−3.919	1.412		−2.775	.006	−6.698	−1.140
Age (years)	.310	.032	.487	9.725	.000	.247	.373
Self-reported asthma	3.476	.788	.214	4.410	.000	1.925	5.027
Smoking	1.930	.959	.098	2.013	.045	.043	3.818
Perennial rhinitis	2.012	1.543	.066	1.304	.193	−1.024	5.048
Perennial+seasonal	2.164	1.023	.116	2.116	.035	.152	4.177
Sensitization (poly vs mono)	2.479	.940	.145	2.637	.009	.629	4.329

[a]Dependent Variable.

Table 3 Multinomial logistic regression model for the clinical pattern of rhinitis.

Type of symptoms[a]	Parameter estimates				
	B	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
				Lower bound	Upper bound
Perennial vs. seasonal					
Intercept	0.974	0.128			
Age	−0.058	0.001	**0.944**	0.912	0.977
Allergic conjunctivitis=Yes	−1.234	0.002	**0.291**	0.134	0.632
Allergic conjunctivitis=No					
Sinusitis=Yes	1.775	0.000	**5.901**	2.239	15.553
Sinusitis=No					
Polysensitisation	−1.146	0.003	**0.318**	0.149	0.680
Monosensitisation					
Perennial with seasonal exacerbation vs. seasonal					
Intercept	−1.236	0.017			
Age	0.002	0.865	**1.002**	0.980	1.024
Allergic conjunctivitis=Yes	−0.216	0.458	**0.806**	0.455	1.425
Allergic conjunctivitis=No					
Sinusitis=Yes	0.971	0.029	**2.640**	1.107	6.297
Sinusitis=No					
Polysensitisation	−0.011	0.973	**0.989**	0.537	1.822
Monosensitisation					

[a]The reference category is: seasonal.

and sinusitis. By contrast, exercise-induced asthma increased almost 6.5 times the frequency of self-reported and 12 times the frequency of documented asthma among patients with rhinitis (Fisher's exact $p<0.001$, odds ratio=6.49 and $p<0.001$, odds ratio=12.25, respectively) (Tables 4a and 4b).

Binary logistic regression has shown that every additional year in duration of rhinitis increases the possibility of self-reported asthma by 5.4% and by 4.1% that of documented asthma.

Survival analysis

Survival analysis for the estimation of asthma onset showed that the time with rhinitis alone reaches a mean time of 16.6 years (median 12 years, incidence 0.0596). The Kaplan-Meier failure estimate curve in Figure 2 presents the estimation of asthma onset in patients with allergic rhinitis.

The mean age that self-reported asthma appears in patients with rhinitis is estimated at 33.7 years (median 34.0 years, incidence 0.0203). The relevant curve is presented in Figure 3.

Table 4a Exercise-induced asthma in patients with allergic rhinitis as a predictive factor of asthma: self-reported asthma.

Asthma symptoms reported * Exercise-induced asthma crosstabulation

	Exercise-induced asthma		Total
	No	Yes	
Asthma symptoms reported			
Yes			
Count	133	22	155
% within Exercise-induced asthma	45.9%	84.6%	49.1%
No			
Count	157	4	161
% within Exercise-induced asthma	54.1%	15.4%	50.9%
Total			
Count	290	26	316
% within Exercise-induced asthma	100.0%	100.0%	100.0%

Fisher's exact p-value <0.001.
Odds Ratio for asthma symptoms (Exercise-induced asthma Yes vs. No) $=6.49$.

Table 4b Exercise-induced asthma in patients with allergic rhinitis as a predictive factor of asthma: spirometrically documented asthma

Spirometric documentation * Excercise-induced asthma crosstabulation

	Exercise-induced asthma		Total
	No	Yes	
Asthma symptoms reported			
Yes			
Count	45	18	63
% within Exercise-induced asthma	15,5%	69,2%	19,9%
No			
Count	245	8	253
% within Exercise-induced asthma	84,5%	30,8%	80,1%
Total			
Count	290	26	316
% within Exercise-induced asthma	100,0%	100,0%	100,0%

Fisher's exact p-value <0.001.
Odds Ratio of Spirometric documentation of asthma (exercise-induced asthma Yes vs. No 12.25).

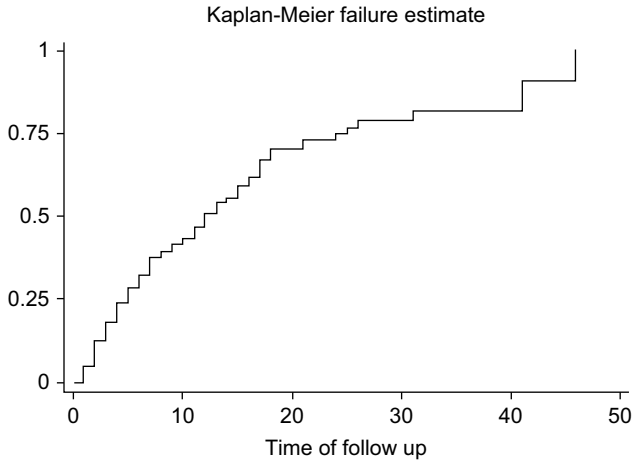

Figure 2 Survival analysis for the time interval of asthma onset in patients with allergic rhinitis.

Figure 3 Survival analysis for the age of asthma onset in patients with allergic rhinitis.

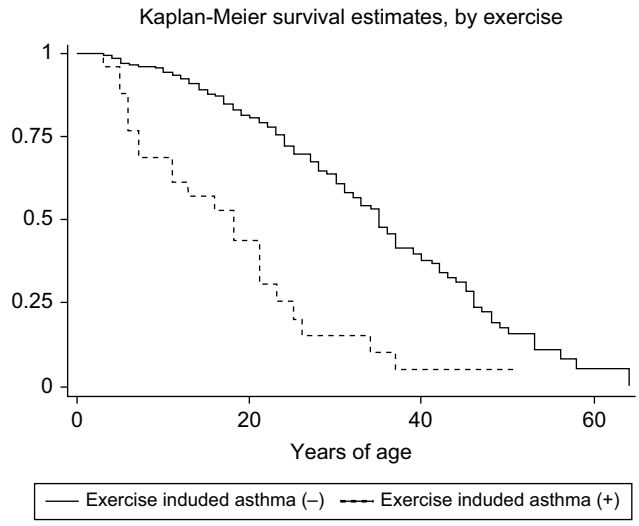

Figure 4 Survival analysis for the age of asthma onset in patients with allergic rhinitis according to the presence of exercise-induced asthma.

The presence of exercise-induced asthma in patients with rhinitis is related to an earlier onset of asthma with a mean age of 18.3 years vs. 35.1 years in patients without exercise-induced asthma ($p<0.001$, incidence 0.0503 vs. 0.0185) as shown in Figure 4.

Discussion

The present study presents the clinical course of allergic rhinitis and its relationship with co-morbidities and especially with asthma in the Mediterranean area, based on data from a tertiary reference Allergy Department. In this context, it was found that the incidence of asthma symptoms in patients with rhinitis is almost 50%, while in almost 20% a diagnosis was documented with spirometry. The duration of rhinitis correlated with the presence of asthma, the pattern of sensitisation and the smoking habit. Furthermore, the duration of rhinitis clearly affects the incidence of asthma as every additional year increases the possibility of asthma by almost 5%.

There are strengths and limitations of the current study that are worth discussing. First of all this study does not represent a prospective study, so the interpretation of the results and the comparisons with other studies must always bear this in mind. On the other hand, the diagnosis of allergic rhinitis was well-documented and all data were obtained with the same procedures. We have to say that our population mostly suffered from persistent moderate to severe rhinitis according to ARIA guidelines; the vast majority of study participants had reported previous visits to other physicians, non-allergists in most cases, for their nasal symptoms.

Previous prospective studies have reported a positive association between rhinitis and asthma in adults[6,9–11]. A study in 1021 college students reported that asthma was three times more likely to develop in those with allergic rhinitis than controls during a 23-year follow up[9]. Another study of people aged 18–45 years in Finland showed that allergic rhinitis was a strong predictor for asthma during a 15-year follow-up[6]. Besides, a longitudinal study of 7-year old children followed-up at the age of 44 years confirmed that even childhood allergic rhinitis increases the incidence of asthma at adulthood[10]. Guerra et al. had already shown an independent association between rhinitis and incident asthma in both atopic and non-atopic adults[8]. Our data are in full accordance with these findings; however, the comparison of the various results is difficult because of the heterogeneous methods used. In our study statistical analysis showed that every additional year in the duration of allergic rhinitis increases the possibility of asthma incidence by 5.4%. The incidence of asthma over 8.8 years of follow-up, in more than 6000 individuals with allergic rhinitis from 14 European countries, participating in the European Community Respiratory Health Survey, was estimated to be 4.4% and was found to be higher than in asymptomatic atopic subjects and in non-allergic rhinitis sufferers[12]. In the same study, it was found that patients with multiple sensitisations and with sensitisation to house dust mites have the highest risk for increased asthma incidence. Besides, a birth cohort study has shown that sensitisation in perennial allergens early in life is a strong predictor of chronic asthma in children[13]. In our study we did not found correlation of asthma incidence with the pattern of sensitisation or with any specific allergen; a possible explanation for this difference could be the heterogeneous characteristics of the study population as almost 70% of study participants suffered from seasonal rhinitis, while in previous studies sensitisation to perennial allergens and perennial rhinitis, was the prevalent clinical pattern.

It is noteworthy that almost 70% (103/165) of patients with self-reported asthma had normal spirometric values. However, our data do not imply necessarily that these patients do not have asthma; the seasonal pattern of respiratory allergy is the most prevalent in Greece and the Mediterranean climate looks friendly for asthma; in these terms, even in the existence of asthma, spirometric values might be normal at certain time points, e.g. out of the pollen season.

In the present study, risk factors for longer duration of rhinitis were found to be: perennial vs. seasonal, multiple sensitisation, asthma and current smoking. The ECRHS study reported that the type of sensitisation, the familiar history of atopy and high levels of total IgE are the most important risk factors for allergic rhinitis and asthma[14]. In the same study, 59.2% of the patients with respiratory allergy were non-smokers or ex-smokers while in our population this proportion reaches 80%. It seems that patients with allergic rhinitis are reluctant to smoke maybe due to the disturbing nasal symptoms or because they are worried about the possible synergistic damage of tobacco smoke and allergic rhinitis to their respiratory system.

In terms of the sensitisation characteristics, in over 60% sensitisation was found to one or more seasonal allergens, with *Parietaria* being the most prevalent allergen; (almost twice as frequent as grasses species). Our findings are totally different than those reported in previous studies such as ECRHS[14]. However, in all multi-centre studies major differences in sensitisation pattern were detected between participating centres even in the same country[15]. In the

whole study population, the most prevalent allergen proved to be house dust mites with a frequency of 21%, followed by grasses (19%). Among patients who were monosensitised the frequencies were: house dust mites 28%, grasses 23% while sensitisation to *Parietaria* as well as to birch pollen reached only 4%. These data clearly depict the strong variation in sensitisation pattern between populations with different characteristics, reflecting the major influence of unique environmental factors upon the clinical features of respiratory allergy.

In conclusion, the present study shows that the unique environmental conditions and the aerobiology of each area clearly affect the clinical features and the temporal association of respiratory allergy; besides, it re-assesses the strong epidemiological association between allergic rhinitis and asthma.

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