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Age at symptom onset and distribution by sex and symptoms in patients sensitized to different allergens

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The aim of our study was to analyze the clinical features, particularly the age at symptom onset, of allergic subjects (asthma and/or rhinitis) on the basis of the etiologic elements (sensitization to various allergens). We identified a group of monosensitized patients and a group of polysensitized patients. Within these groups, we identified subgroups of subjects monosensitized to one of the five main allergenic mixes (mites, Gramineae, trees, *Parietaria*, and *Artemisia*) and five subgroups of patients sensitized nonexclusively, that is, polysensitized, to the same allergens. The comparison between the two groups and among the various subgroups enabled us to conclude that:

1) mono- and polysensitized patients present some clinical features so different as to constitute two clearly distinct clinical groups
2) analysis of the clinical features associated with the sensitization to a specific allergen brings us to significantly different conclusions when we consider subgroups of monosensitized or polysensitized patients
3) the parameter "age at symptom onset" shows great heterogeneity among both the mono- and the polysensitized subgroups – in particular, the great differences in mean age among the monosensitized subgroups (trees>*Artemisia*>*Parietaria*>Gramineae>mites) appear very interesting and are open to various interpretative hypotheses
4) unlike the polysensitized group, in the monosensitized group and subgroups, mean age is similar between men and women and, only for tree- and *Parietaria*-monosensitive patients, also between asthmatic and rhinitic subjects.

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Age at symptom onset is a clinical parameter widely studied in allergic respiratory diseases. However, it is generally analyzed according to the classical distinction between allergic and nonallergic patients, or according to the clinical symptoms (asthma, rhinitis, or asthma plus rhinitis).

Studies analyzing clinical features – in particular, the patients' age – on the basis of etiologic elements, that is, sensitization to different allergens, are less common. Such studies are usually epidemiologic surveys that investigate random samples of the population, and in which the sensitizations may be clinically irrelevant (1–3). Other studies investigate selected patients attending a specific medical center ("influx studies"). In such a setting, they generally consider the overall action of the different allergens without identifying monosensitized patients' groups (4), or are carried out with different aims (5, 6). Studies which specifically analyze the clinical features of selected monosensitized patients are few and they almost always examine only one allergen (5, 7–9).

On the other hand, the heterogeneity of the criteria for subject selection (random unselected samples or patients? what kind of patients?) and, often, of the clinical features themselves (age at symptom onset, age at research time, age at first visit, etc.) in these various studies indicates the need to compare the clinical effects of the different allergens in a single study.

Our study aimed to analyze the clinical features, particularly the age at symptom onset, of allergic patients monosensitized to different allergens. Monosensitization was, in fact, the clinical characteristic that enabled us to isolate the effect of a single allergen from those of other allergens and to compare that effect in different social-geoclimatic environments. To test the validity of this assumption, we also compared the clinical features of mono- and polysensitized patients.

Material and methods

Patients and skin prick test (SPT)

We considered patients, aged 3–74 years (mean age 26.8 years), suffering from asthma and/or rhinitis, examined during the last 5 years in the Allergological Center of Bergamo, a city located in northern Italy in the Padana plain at the mouth of the Pre-alpine Brembana and Seriana valleys.

During diagnostic procedures, the patients underwent an anamnestic questionnaire and SPTs. Glycerinate extracts (Lofarma Pharmaceutical Laboratory, Milan, Italy) of the following allergenic sources were used in SPTs: house-dust mites (*Dermatophagoides farinae* and *D. pteronyssinus*), molds (*Alternaria*, *Aspergillus fumigatus* and *As. niger*, and *Cladosporium*), cat and dog dander, Gramineae (mix), *Parietaria officinalis*, trees (*Betula*, *Corylus*, and *Alnus*), *Artemisia vulgaris*, and *Plantago Lanceolata*. In addition to these allergens, skin tests for other allergens considered clinically relevant in single cases were performed on occasion. All the extracts were at 4% concentration. Positive (histamine 10 mg/ml) and negative (saline solution) controls were included. Reactions were evaluated 20 min after the performance of the test. In our study, we considered positive only skin reactions equal to or greater than the histamine wheal.

Monosensitized allergic patients and polysensitized allergic patients

Among the tested patients, we identified allergic subjects monosensitized to one of the five main allergenic mixes: mites, Gramineae, trees, *Parietaria*, and *Artemisia* (in the tree mix, we considered birch, hazel, and alder because of their well-known cross-reactivity) (10, 11). To define "allergic monosensitized subject", we fixed a highly selective criterion: the presence of a positive prick test for only one allergen was not considered sufficient, but the recorded sensitization (equal to or greater than the histamine wheal) was also required to be unassociated with any other reaction of ≥25% of the histamine wheal and to agree with seasonal or perennial recurrence of the symptoms; thus, the presence of the symptoms had to be explained by the contact with that specific allergen. Therefore, we excluded from our analysis 85 monosensitized patients with a recurrence of symptoms not in agreement with the recorded monosensitization and 586 patients with only one sensitization equal to or greater than the histamine wheal but with one or more other reactions of ≥¼ the histamine wheal.

Similarly, we identified the allergic subjects sensitized to the same allergens, but not exclusively to only one of them (that is, the polysensitized patients).

In this study, we use the term "groups" to indicate all the monosensitized patients or all the polysensitized patients; "subgroups" to indicate patients monosensitized to one specific allergen (for example, the subgroup of mite-monosensitive patients) or patients sensitized to that specific allergen in addition to other allergens (for example, the subgroup of mite-polysensitive patients). Obviously, the monosensitized subgroups include distinct patients, while the same polysensitized patient can be included in several polysensitized subgroups.

Statistical analysis

Differences among means were assessed by nonparametric tests (Mann–Whitney test and Kruskal-Wallis test). The confidence intervals were calculated with Student's t distribution. Proportions were compared by the chi-square test. In particular, for better assessment of the relationship between a specific kind of sensitization and the risk of developing asthmatic symptoms, in statistical analyses relative to symptom distribution, we considered "asthma with rhinitis" and "asthma without rhinitis" together, comparing, in this way, only the symptoms "asthma, with or without rhinitis" and "rhinitis only". A two-tailed P value of 0.05 was chosen as the limit of significance in all the tests.

Results

The clinical features of the groups of the monosensitized and polysensitized allergic patients as a whole are compared in Table 1. In comparison of the former group with the latter:

1) the male/female ratio, even if also, in this case, higher than 1, was lower ($P<0.05$)
2) the prevalence of asthmatic symptoms was, on the whole, less relevant ($P<0.005$), although the rate of asthmatics without rhinitis was much higher (polysensitization, on the other hand, more often induced the presence of both the diseases: asthma plus rhinitis)

Table 1. Clinical features (distribution by sex, symptoms, and age at symptom onset) of mono- and polysensitized patients. Statistical comparison between two groups

	n	M/F	Asthma only	Asthma plus rhinitis	Rhinitis only	Mean age (years)	95% CI
Monosens. patients	541	1.03	10.7%	29.8%	59.5%	21.89	(20.70–23.08)
Polysens. patients	1053	1.35	5.6%	42.5%	51.9%	16.69	(15.98–17.39)
P		<0.05		<0.005		0.0000	

3) mean age at symptom onset was significantly higher (P=0.0000).

The clinical features of the subgroups of the patients monosensitized to the five main allergenic mixes are analyzed one by one and compared in Table 2. The distribution by sex, within the overall prevalence of the male sex (with the sole exception of trees), did not show statistically significant differences, while the symptom distribution was significantly different among the various subgroups (P<0.05). In this respect, heterogeneity of symptom distribution appeared to be more relevant in considering the symptom "asthma only" separately from "asthma plus rhinitis". Sensitizations to mites and trees were, in fact, more often associated, on the whole, with asthma symptoms, but the former subgroup showed very high rates for asthmatics without rhinitis, and the latter for asthmatics with rhinitis. In this respect, it should be also pointed out that in the *Parietaria* subgroup no patient suffered from asthma without rhinitis.

However, age at symptom onset is the parameter that probably shows the most interesting variability among the different subgroups (P=0.0000), as is also underlined by the comparison among the distributions by age classes of the four main monosensitized subgroups shown in Fig. 1.

The data of the five subgroups of the polysensitized patients are summarized in Table 3. The distribution by sex was homogeneous. On the contrary, rates related to symptom distribution showed some differences. In this case also, as for monosensitized patients, the mite subgroup had the highest percentage of asthmatics without rhinitis and the trees subgroup the highest percentage of asthmatics with rhinitis, but the variability of the values among polysensitized subgroups appeared, on the whole, to be less relevant than among monosensitized subgroups. This greater homogeneity was confirmed by statistical comparison based on the presence of asthma symptoms (P: NS). Finally, age at symptom onset was again a very heterogeneous parameter (P=0.0000). The statistically significant differences between the mono- and polysensitized patients subgroups relative to each allergen are also reported in Table 3. It is remarkable that the mean age at symptom onset in the subgroups of polysensitized patients appeared to be in all cases significantly lower than in the respective subgroups of monosensitized patients. Moreover, the heterogeneity of the age at symptom onset is underlined in Fig. 2, where the 95% confidence intervals (CIs) of the main subgroups, both mono- and polysensitized, are compared.

Finally, by processing the data of each subgroup in relation to sex and symptoms (Table 4), we found that

1) while, in the polysensitized subgroups (with the sole exception of the *Parietaria* subgroup), the age at symptom onset was significantly lower for men than for women, in the monosensitized subgroups there were no significant differences
2) there was no correlation between asthma symptoms (with or without rhinitis) and an earlier age of onset only for trees- and *Parietaria*-monosensitive patients.

When we considered the groups of mono- and polysensitized patients as a whole (Table 5), increasing, in this way, the sample size and the power of the test, the results were confirmed. In Table 5, the mean ages of asthmatics without

Table 2. Clinical features (distribution by sex, symptoms, and age at symptom onset) of monosensitized subgroups. Statistical comparison among five subgroups

	n	M/F	Asthma only	Asthma plus rhinitis	Rhinitis only	Mean age (years)	95% CI
Mites	271	1.08	17.0%	28.8%	54.2%	17.61	(16.01–19.20)
Gramineae	121	1.05	5.0%	27.3%	67.8%	18.72	(16.60–20.85)
Trees	98	0.75	5.1%	38.8%	56.1%	35.72	(33.58–37.86)
Parietaria	34	1.12	–	26.5%	73.5%	23.53	(20.95–26.11)
Artemisia	17	1.83	5.9%	17.6%	76.5%	29.59	(22.10–37.08)
P		NS		<0.05		0.0000	

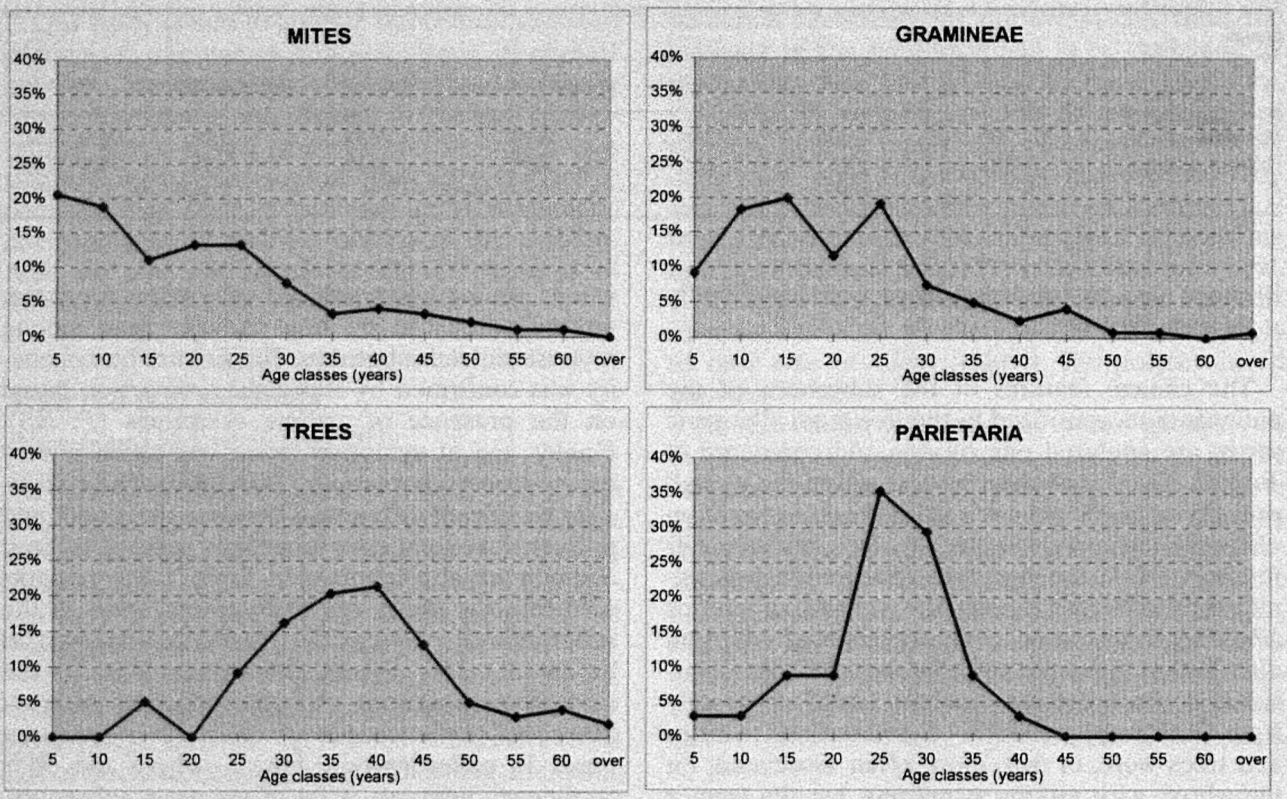

Fig. 1. Distribution by age at symptom onset in subgroups monosensitized to mites, Gramineae, trees, and *Parietaria*.

rhinitis and of asthmatics with rhinitis are also shown. The former was much lower in both groups.

Discussion

The results of our study indicate that mono- and polysensitized patients present clinical features so different as to constitute two clearly distinct clinical groups. All considered parameters show statistically significant differences that, even if scarcely comparable with previous studies, are in line with data already published (2, 12–14).

Considering symptom and age distribution, we found among the subgroups of monosensitized patients a larger heterogeneity than among the subgroups of polysensitized patients (heterogeneity confirmed by the scant literature on this matter [9, 14, 15]). In particular, the mean ages at symptom onset proved to be significantly different also among polysensitized subgroups, but less clearly than among monosensitized subgroups. In fact, as illustrated in Fig. 2, the mean values of the polysensitized subgroups were more clustered than those of the monosensitized subgroups (15.94–18.66 years *vs* 18.65–35.64 years). In particular, although trees- and *Parietaria*-monosensitized subgroups showed large 95% CIs, they were distinctly separate from the other subgroup CIs. This greater

Table 3. Clinical features (distribution by sex, symptoms, and age at symptom onset) of polysensitized subgroups. Statistical comparison among five subgroups

	n	M/F	Asthma only	Asthma plus rhinitis	Rhinitis only	Mean age (years)	95% CI
Mites	431	1.36	8.8%	43.4%	47.8%	13.99[d]	(12.93–15.04)
Gramineae	886	1.41	5.8%[e]	43.3%[e]	50.9%[e]	15.52[c]	(14.80–16.23)
Trees	448	1.50[b]	2.5%	50.2%	47.3%	18.55[f]	(17.42–19.67)
Parietaria	306	1.47	3.3%[a]	46.1%[a]	50.7%[a]	18.72[c]	(17.46–19.98)
Artemisia	271	1.53	3.7%	41.0%	55.4%	19.19[c]	(17.65–20.73)
P		NS	←	→	NS ←	0.0000	

Superscript letters refer to statistical comparison between value of subgroup of polysensitized patients and correspondent value (shown in Table 2) of subgroup of patients monosensitized to same allergen, with following meaning:
[a]$P<0.05$; [b]$P<0.01$; [c]$P<0.005$; [d]$P<0.001$; [e]$P<0.0005$; [f]$P=0.0000$.

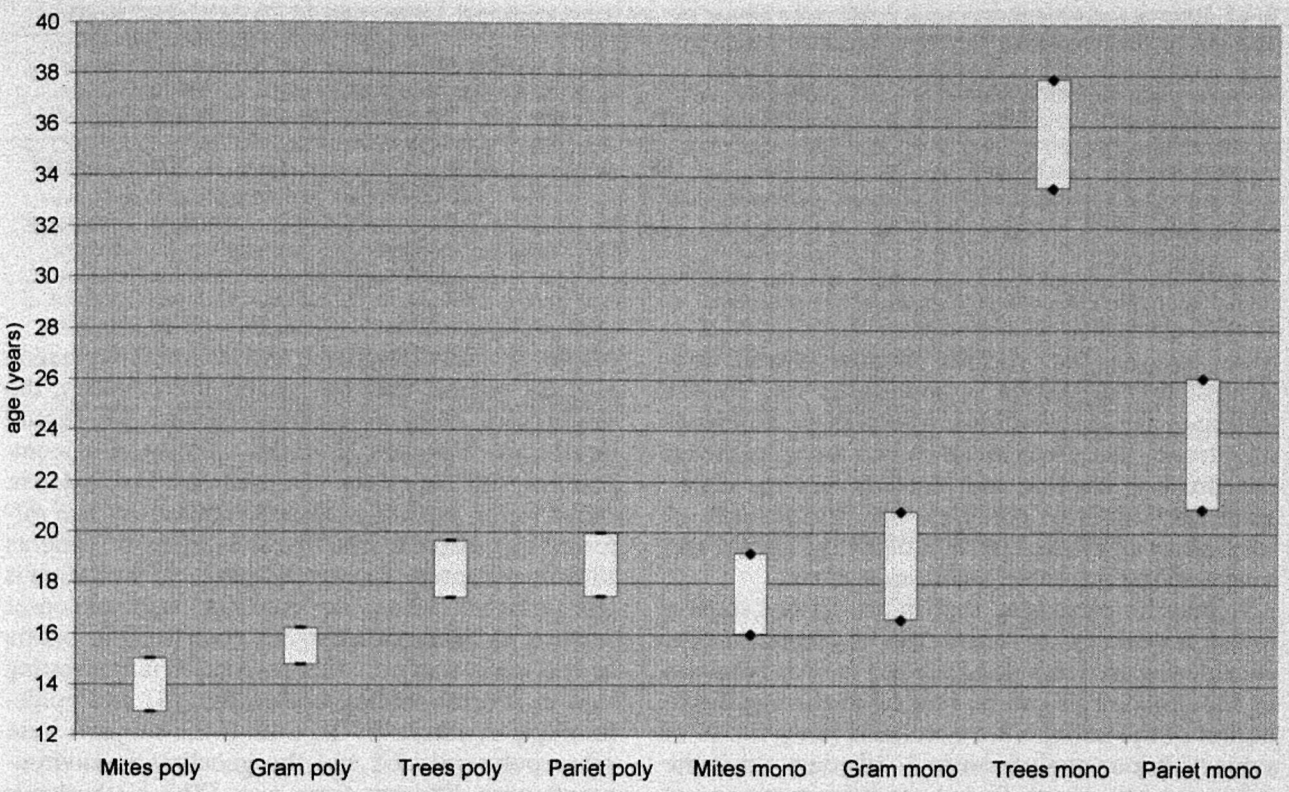

Fig. 2. Mean age. 95% confidence intervals of main, both mono- and polysensitized, subgroups. *Artemisia* subgroups have been omitted because of limited number of *Artemisia*-monosensitive patients.

homogeneity among the polysensitized subgroups was not so unexpected in view of the fact that, unlike the monosensitized subgroups, they comprise patients who, as they show sensitizations to more than one allergen, are often included in several subgroups.

However, these data suggest that, in order to understand and distinguish the clinical features correctly on the basis of etiologic elements (that is, the sensitization to different allergens), it is necessary to analyze monosensitized patients. In fact, in these patients the lack of a multiplicity of sensitizations does not mask and confuse the clinical effects of the different allergens. This conclusion is also confirmed by the numerous statistically significant differences between the subgroups of patients mono- and polysensitized to each allergen, differences that are also partially present in other studies (between birch-monosensitive and birch-polysensitive patients [5], and between cypress-monosensitive and cypress-polysensitive patients [7]).

Moreover, within the single monosensitized subgroups, we recorded a great homogeneity (with very close averages) of mean age between men and women, and, for trees and *Parietaria*, between asthmatics and rhinitics, a homogeneity that we did not find within the polysensitized subgroups.

However, in our opinion, the most interesting data refer to the variability of mean age at symptom

Table 4. Statistical comparison of mean age at symptom onset between men and women and between asthmatics (with or without rhinitis) and rhinitics (without asthma) within each subgroup (*Artemisia* subgroups have been omitted because of limited number of *Artemisia*-monosensitive patients)

	Mean age (years) Male		Mean age Female	*P*	Mean age Asthma		Mean age Rhinitis	*P*
Mites-monosens.	17.41	*vs*	17.82	NS	15.27	*vs*	19.58	<0.001
Gramineae-monosens.	18.15	*vs*	19.32	NS	14.74	*vs*	20.64	<0.005
Trees-monosens.	35.05	*vs*	36.23	NS	35.88	*vs*	35.60	NS
Parietaria-monosens.	23.89	*vs*	23.12	NS	22.11	*vs*	24.04	NS
Mites-polysens.	12.19	*vs*	16.40	<0.0005	12.28	*vs*	15.92	0.0000
Gramineae-polysens.	14.22	*vs*	17.35	0.0000	13.87	*vs*	17.11	0.0000
Trees-polysens.	16.84	*vs*	21.07	<0.001	17.07	*vs*	20.20	<0.005
Parietaria-polysens.	18.09	*vs*	19.63	NS	16.97	*vs*	20.46	<0.01

Table 5. Statistical comparison of mean age at symptom onset between men and women and between asthmatics and rhinitics in each of two groups

	Mean age (years) Male		Mean age Female	P	Mean age Asthma only	Plus Rhinitis		Mean age Rhinitis only	P
Monosens. patients	21.23	*vs*	22.57	NS	19.95 (16.12	21.33)	*vs*	23.22	<0.0005
Polysens. patients	15.25	*vs*	18.62	0.0000	14.95 (11.96	15.33)	*vs*	18.31	0.0000

onset among the various monosensitized subgroups; this variability is underlined also by the different age distributions. Mites show a descending trend, like Gramineae (which have, however, two drops in the first and fourth 5-year age class), while the slopes of *Parietaria* and, particularly, of trees show an evident peak in older age classes and more closely resemble a Gaussian curve.

It may be surprising that mites do not show a lower mean age of onset and a steeper slope, considering that this sensitization is very common in childhood. This can be related to the age distribution of the patients we examined (only 15.4% of subjects in our analysis were 1–10 years old at the moment of the visit); in any case, the mean age of onset of mite-polysensitive patients was considerably lower (13.99 years).

However, the curve of trees is probably the most interesting, affecting very old age classes, an unusual effect in allergic diseases. In this respect, it appears peculiar that none of the 98 trees-monosensitive patients had symptom onset in the first 10 years of life, and only 5.1% in the first 20 years (compared to 63.8% of mites-, 59.2% of Gramineae-, and 23.5% of *Parietaria*-monosensitive patients).

The causes of these differences of age of onset among the various allergens may include conformational factors (different size or structure of pollens, different characteristics of the biologic aerosols, differences in airways size, etc.), environmental factors (e.g., different atmospheric concentration of pollens), and behavioral factors (e.g., less frequent outdoor exposure during childhood).

Comparison with previous studies carried out in different geoclimatic environments certainly does not solve the problem, particularly in the light of the extreme methodological variability of these studies. In some cases, the mean ages relative to the different allergens were close to those we recorded or, at least, were distributed in a similar way (in Naples [15], for *Parietaria* and mites; in Salamanca [9] and Emilia-Romagna [14], for Gramineae and *Artemisia*), underlining the importance of the kind of allergen; in other cases, these mean ages differed to a greater or lesser extent from ours (the values were evidently higher in Naples [15] for Gramineae and in Emilia-Romagna [14] for mites), underlining, on the contrary, the importance of environmental factors. We should point out, however, that the validity of a comparison with the values of age of onset recorded in other influx studies is greatly limited by the different age distributions of the samples of patients they investigated. This methodological limitation is less relevant when we consider ages of onset relative to different allergens compared to others in the same study. In this respect, it is interesting that in several studies, both influx (4) and epidemiologic in nature (1–3), even if the subjects were often polysensitized and the geoclimatic environments very different from ours (The Netherlands [2], Scandinavia [1, 3], and Missouri, USA [4]), sensitization to Betulaceae appeared to be spread over classes of older ages than that to Gramineae.

Therefore, it is difficult to draw definitive conclusions on the matter. In fact, we can assume a link between extensive environmental exposure to the allergen and early onset of symptoms, but this does not seem to apply always. In view of these contradictory indications, it seems likely that several different elements can influence early or delayed sensitization and, therefore, the onset of allergic symptoms. In this respect, we conclude by underlining the importance of comparative multicentric studies for a better understanding of the issue.

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