On the Association between Date of Birth and Pollen Sensitization: Is Age an Effect Modifier?

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ABSTRACT

An association between date of birth and development of allergy has been proposed by prior research. Yet, the presence of a dose–response relationship or any potential effect modification for this association has not been widely studied. The aims of our study were to investigate whether an association between birth during pollen season and symptomatic sensitization to pollens exists, whether this association is stronger for patients with high rather than low allergic reactivity to pollens, and whether this association is modified by the age of the patients. Among 3318 asthmatic and/or rhinitic outpatients, we selected 805 patients sensitized exclusively to pollens (78 with low reactivity [LR] and 727 with high reactivity [HR]) and 629 patients with negative skin-prick tests (SPT) (control group). The association between being born during pollen season (February–July) and each of the pollen reactivity levels was assessed by estimating the odds ratios (OR). HR pollinosis patients were more likely than SPT negative patients of being born in February–July (OR 1.38, 95% Confidence Intervals (CI) 1.11–1.71). The likelihood of having been born in pollen season significantly increased across the levels of reactivity to pollens (HR > LR > SPT negative). These findings were valid only among patients with an early onset of symptoms. Although the OR for being born in pollen season was 1.91 (95% CI 1.32–2.77) for HR pollinosis patients with onset of symptoms ≤15 years, it was 1.13 (95% CI 0.87–1.48) for those with later onset of symptoms (test of homogeneity: p = 0.026). Our results suggest that the exposure to allergenic pollens in the first months of life increases the risk of developing clinically relevant sensitization to them, particularly in the first 15 years of life. (Allergy and Asthma Proc 23:303–310, 2002)

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Genetic predisposition is recognized to play a central role in the development of atopic disease. However, the interaction of genetics with environmental factors and the timing of environmental exposure are critical in explaining how and why the disease actually appears. Environmental factors are being widely investigated not only to better understand the pathogenesis of allergy, but also because, to date, their control is considered essential in most experimental programs of primary, secondary, and even tertiary prevention.[1–3] In this respect, the association between date of birth and development of allergy holds a particular interest because of the very early timing of the exposure.

Date of birth has been associated with allergic sensitization to seasonal,[4–11] perennial,[4,8,12,13] and food allergens,[4,14] as well as with the onset of respiratory symptoms and eczema.[5,15–18] The role of potential nonallergen-related mechanisms has been hypothesized for some of these associations. Nevertheless, the early exposure to allergens appears the most likely explanation for the effect of the season of birth on allergic sensitization, especially in the case of pollens that are present only during specific periods of the year.

Although some investigators failed to find any relationship,[19,20] the association between month of birth and allergic sensitization to pollens has been confirmed by most studies.[4–11] Schäfer et al.[19] were unable to find any association between month of birth and grass or birch sensitization

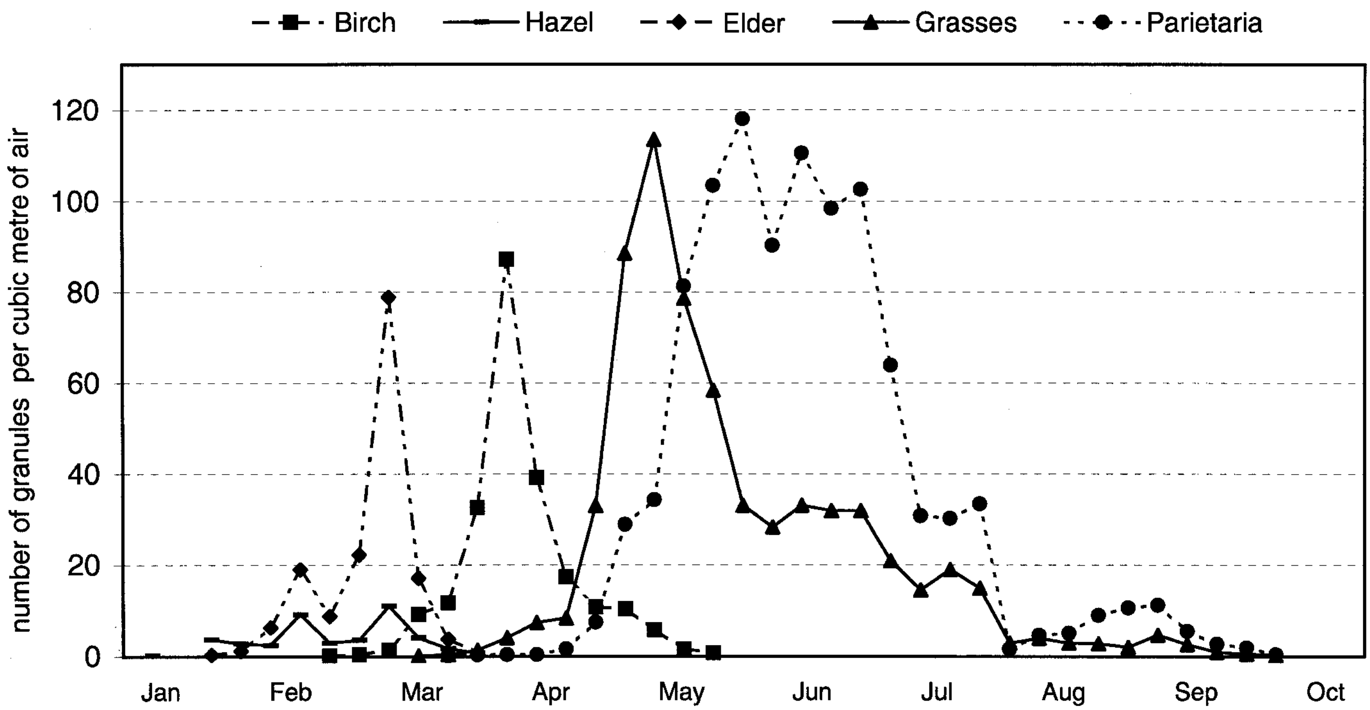

Figure 1. Pollen count for grasses, trees, and Parietaria *in Milan (~30 miles from Bergamo). The values are the means of counts collected in 1985, 1986, 1995, and 1996. (Thanks to the kind collaboration of Laboratorio Farmaceutico Lofarma s.r.l., Milano, Italy)*

among 1066 Bavarian preschool children. However, their findings could have been affected by the small number of atopic subjects in the study population. In a larger sample of 6535 10-year-old children in Munich and Southern Bavaria, Wjst et al.[5] found an increased risk of developing skin sensitization to grass pollen for subjects born in February, May, or June. Similarly, in a study carried out in Amsterdam, Aalberse et al.[4] could confirm the influence of the month of birth on the chance of developing IgE antibodies to grass and birch. The sample size was very large (150,000), and the relative risks for developing IgE to seasonal and nonseasonal allergens showed regular fluctuations across the months. Previous studies have shown that the month of birth was associated with allergy to birch pollen among Finnish patients[7] and with ragweed sensitization among US college students born in states where ragweed was present in relevant concentrations.[11]

Several reports have also correlated birth during pollen season to pollen sensitization in Italy. Carosso et al.[9] found that pollinosis patients sensitized to grasses were more likely to have been born in March–June (grass pollen season in Turin) than patients sensitized to house dust. Interestingly, the association was valid only among subjects born in northern Italy. Similarly, in a study carried out in Rome, Businco et al.[8] found that a higher proportion of children sensitized to grasses were born in March–May as compared with the total live birth distribution in the Rome district.

In most studies, the presence of atopy has been defined according to a specific cut-off point: specific dimension of the wheal for skin-prick tests or specific level of IgE. However, allergy can be investigated also from a quantitative point of view. Measures such as the number of skin sensitizations, the dimension of the wheal, and the level of IgE are, by nature, continuous or discrete rather than dichotomous variables. Specifically, it could be hypothesized that patients showing high degrees of allergic reactivity are more likely to have been born in months of maximum exposure to allergens than patients with lower degrees of allergic reactivity (dose–response relationship). Yet, such distinction has rarely been used.[21]

Although the exposure to allergens in the first months of life is likely to affect the development of an allergic sensitization in young rather than old age, few studies[7,12,22–24] have addressed this age-related issue as well. If this hypothesis were true, in a retrospective study design like ours, the association between date of birth and allergic sensitization would be expected to be stronger in young patients or in patients with an early onset of symptoms.

The aims of our study were to investigate whether an association between symptomatic sensitization to pollens and birth in pollen season existed and whether this association showed a dose–response relationship and was modified by the age of the patients.

MATERIALS AND METHODS

Study Population

Our study population consisted of 3318 outpatients (mean age 26.6 years) suffering from asthma, rhinitis, or both, examined at the Allergy Medical Center in

TABLE I

Distribution by Date of Birth of SPT-negative, LR, and HR Pollinosis Patients

	Born in February–July *n* (%)	Born in August–January *n* (%)	Odds Ratio	95% Confidence Interval	*p* Value
SPT-negative patients	294 (46.7%)	335 (53.3%)	1.00		
LR pollinosis patients	41 (52.6%)	37 (47.4%)	1.26	0.79–2.02	NS
HR pollinosis patients	398 (54.7%)	329 (45.3%)	1.38	1.11–1.71	0.004

The ORs, the 95% CIs, and the p value refer to the association with birth in February–July.
Test for trend: p = 0.003.
Pollinosis patients were classified as LR if their largest wheal was + or ++. They were classified HR if their largest wheal was +++ or ++++.

TABLE II

Odds Ratio, 95% CI, and *p* Value Associated with the Variables "Largest Wheal" (from − to ++++) and "Number of Sensitizations" (from zero to three) in Two Separate Logistic Regressions with "Birth in Pollen Season" as Dependent Variable

Variable	Odds Ratio*	95% Confidence Interval	*p* Value
Dimension of the largest wheal	1.09	1.03–1.15	0.004
Number of sensitizations	1.15	1.04–1.28	0.008

**The ORs refer to the likelihood of being born in pollen season associated with an increase by one level of the dimension of the largest wheal (as from ++ to +++) and of the number of sensitizations (as from one to two).*

Bergamo, Italy. We used data directly collected from medical charts. Demographic and clinical variables, including the age at the time of the visit and the age at the onset of respiratory symptoms (when asthma or rhinitis first appeared) were recorded for each patient.

During diagnostic procedures, the patients underwent skin-prick tests (SPT). For SPT, glycerinated extracts (Lofarma Pharmaceutical Laboratory, Milan, Italy) of the following allergenic sources were used: house-dust mites (*Dermatophagoides farinae* and *pteronyssinus*), molds (*Alternaria*, *Aspergillus fumigatus* and *niger*, *Cladosporium*), cat and dog dander, grasses (mix), trees (*Betula*, *Corylus*, and *Alnus*), *Parietaria officinalis*, *Artemisia vulgaris*, and *Plantago lanceolata*. All the extracts were at a 4% concentration. Positive (histamine 10 mg/mL) and negative (saline solution) controls were included. Reactions for each allergen were compared to the histamine wheal (HW) 20 minutes after conducting the test and categorized into five increasing levels (−, +, ++, +++, ++++).[25] Reactions smaller than ¼ of the HW were recorded as negative (−). Positive reactions were categorized as +, ≥¼ HW and <½ HW; ++, ≥½ HW and <1 HW; +++, ≥1 HW and <2 HW; or ++++, equal to or greater than twice the HW.

Subject Selection

Among our study population, we selected 917 patients sensitized to grasses and/or *Parietaria* and/or trees and not sensitized to mites or animal danders (pollinosis patients). Only a small proportion of them (7.6%) was also sensitized to molds. Among pollinosis patients, we excluded 112 patients born in different geographical areas. The remaining 805 pollinosis patients were divided into low reactivity (LR) and high reactivity (HR) groups according to the largest wheal for pollens recorded at SPT. Seventy-eight pollinosis patients showing the largest wheal, ≤++, were classified as LR, whereas 727 pollinosis patients with the largest wheal, ≥+++, were classified as HR.

We also identified 702 patients without any positive reaction to any of the tested allergens (SPT negative patients). After excluding 73 patients born in different geographical areas, our control group included 629 SPT negative patients.

Statistical Analysis

This is a case-control study design with pollinosis patients being the cases and SPT negative patients the controls. Two different levels of allergic reactivity to pollens were identified among pollinosis patients: LR and HR. The strength of the association between birth in pollen season and each of the pollen reactivity levels was quantified by estimating the Odds Ratio (OR) and tested for statistical significance using 95% Confidence Intervals (CI).

In addition, using logistic regressions, we investigated the effect of two discrete predictors ("largest wheal" and "number of sensitizations") on the probability of having been born during pollen season (dependent variable). The largest wheal referred to the largest reaction recorded at SPT among those for the three main pollen mixes (grasses, *Parietaria*, and trees). The value ranged from zero (−) to four (++++). The number of sensitizations referred to the total number of main pollen mixes with a positive wheal.

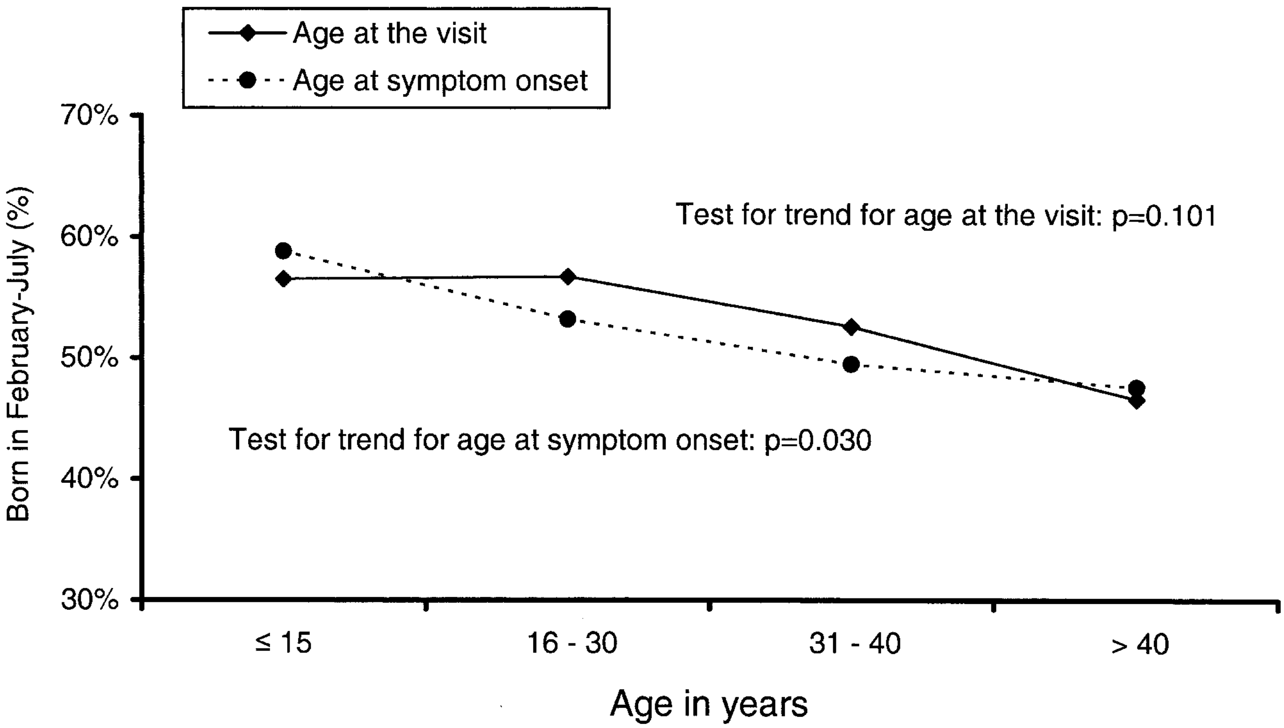

Figure 2. *Proportion of pollinosis patients born in February–July according to the age at the visit and the age at symptom onset.*

The value ranged from zero (SPT negative patients) to three (positive wheals for all the three mixes).

To test the presence of potential effect modifiers or confounders in the association between birth in pollen season and HR pollen sensitization, stratification was performed according to the Mantel–Haenszel method. The presence of effect modification was detected through the test for homogeneity, testing the null hypothesis that the ORs in the different strata were equal. An $\alpha = 0.05$ level of significance was chosen for all the performed statistical tests.

RESULTS

Grasses, *Parietaria*, and trees are the three most important allergenic pollens in Bergamo. The pollen count in Fig. 1 refers to data collected in Milan, a city located ~30 miles away from Bergamo with similar aero-biologic conditions. The pollen count shows that, in our area, the great majority of tree, grasses, and *Parietaria* pollens are present in the period between February and July, which represents the main pollen season, although other secondary pollens can be present in other months.

Table I lists the proportion of patients born in the pollen season according to their SPT status. HR pollinosis patients were 38% more likely to be born between February and July than SPT negative patients (OR 1.38, 95% CI 1.11–1.71), whereas the OR for LR pollinosis patients, although still higher than 1, was no longer significant (OR 1.26, 95% CI 0.79–2.02). The linear trend in the odds ratios across the levels of pollen reactivity was significant (test for trend: $p = 0.003$).

In logistic regression analyses, both the largest wheal and the number of sensitizations proved to be significant predictors of the probability of being born in February–July (Table II). As the largest wheal increased by one level (for example, from ++ to +++), the probability of being born during pollen season increased by 9%. Similarly, the increase by one unit of the number of positive pollen allergens (for example, from one to two) was associated with a 15% increased probability.

Figure 2 shows the distribution of the proportion of pollinosis patients born in pollen season both by the age at the time of the visit and by the age at symptom onset. In both the analyses, the younger the age is, the more likely the pollinosis patients are to have been born in February–July. However, the test for trend is significant only for age at symptom onset, and not for age at the visit.

Consequently, in Table III the association between birth in pollen season and HR pollen sensitization is tested separately for patients with early (≤15 years) and late (>15 years) onset of symptoms. In the former group, the OR is high and significant (OR 1.91, 95% CI 1.32–2.77), whereas in the latter it is not (OR 1.13, 95% CI 0.87–1.48). The association is valid only for patients with an early onset of symptoms. The difference between the two ORs is significant, as confirmed by the test of homogeneity ($p = 0.026$).

Similarly, as shown in Table IV, the dimension of the largest wheal and the number of sensitizations were signif-

TABLE III

Distribution by Date of Birth of HR Pollinosis and SPT-negative Patients in the Strata of Patients with Age at Symptom Onset ≤15 Years and >15 Years

Age at Symptom Onset	February–July *n* (%)	August–January *n* (%)	OR	95% CI	Test of Homogeneity
≤15 years					
HR pollinosis patients	179 (60.3%)	118 (39.7%)	1.91	1.32–2.77	0.026
SPT-negative patients	81 (44.3%)	102 (55.7%)			
>15 years					
HR pollinosis patients	219 (50.9%)	211 (49.1%)	1.13	0.87–1.48	0.026
SPT-negative patients	213 (47.8%)	233 (52.2%)			

The ORs and the 95% CIs refer to the association between birth in February–July and pollen sensitization within each stratum. The test of homogeneity tests the null hypothesis that the two ORs are equal.

TABLE IV

Odds Ratio, 95% CI, and *p* Value Associated with the Variables "Largest Wheal" (from − to ++++) and "Number of Sensitizations" (from zero to three) in Separate Logistic Regressions with "Birth in Pollen Season" as Dependent Variable

Age at Symptom Onset	Variable	Odds Ratio	95% Confidence Interval	*p* Value
≤15 years	Dimension of the largest wheal	1.19	1.08–1.31	0.001
	Number of sensitizations	1.37	1.14–1.63	0.001
>15 years	Dimension of the largest wheal	1.04	0.96–1.11	0.336
	Number of sensitizations	1.03	0.90–1.18	0.651

The results are shown separately for patients with age at symptom onset ≤15 years and >15 years.

icant explanatory variables of the probability of being born in February–July only for patients with an early onset of symptoms (first 15 years of life). In contrast, in the group of patients with late onset of symptoms, neither of these variables was significant.

These results are illustrated in Fig. 3, where the percentage of subjects born in February–July among patients with early and late onset of symptoms is plotted against the dimension of the largest wheal (upper graph) and the number of pollen sensitizations (lower graph). The increasing trend is evident for patients with early onset, but it is not for patients with late onset.

Table V shows that, unlike the age at symptom onset, neither the type nor the duration of symptoms proved to be effect modifiers of the association between date of birth and HR pollen sensitization. Similarly, the association was homogeneous among males and females. None of the variables considered acted as confounders.

Interestingly, the effect on pollen sensitization of being born in pollen season was stronger among subjects born in the months of February and March. The OR for the association between being born in February or March and HR pollinosis, in fact, was 1.74 (1.28–2.36), a value relevantly higher than 1.38, the OR referring to the whole pollen season (from February to July).

Finally, we compared the distribution by month of birth between the groups of HR pollinosis patients with early and late onset of symptoms. We found the percentage of subjects born in pollen season significantly higher for pollinosis patients with early onset of symptoms than for pollinosis patients with late onset of symptoms (60.3% versus 50.9%; OR 1.46, 1.08–1.97).

DISCUSSION

The period between February and July is the main pollen season in the Bergamo area. We can assume that patients born during this period were exposed in the first months of life to higher concentrations of the three main allergenic pollen mixes (grasses, *Parietaria*, and trees) than those born outside this interval.

In our study, only patients with high levels of allergic reactivity to pollens were more likely than controls to have been born during pollen season. A dose–response relationship appeared to exist, because patients with low reactivity to pollens showed odds ratios intermediate between SPT negative and HR pollinosis patients (significant test for trend), and the association with birth in February–July strengthened as the dimension of the largest wheal and the number of sensitizations increased.

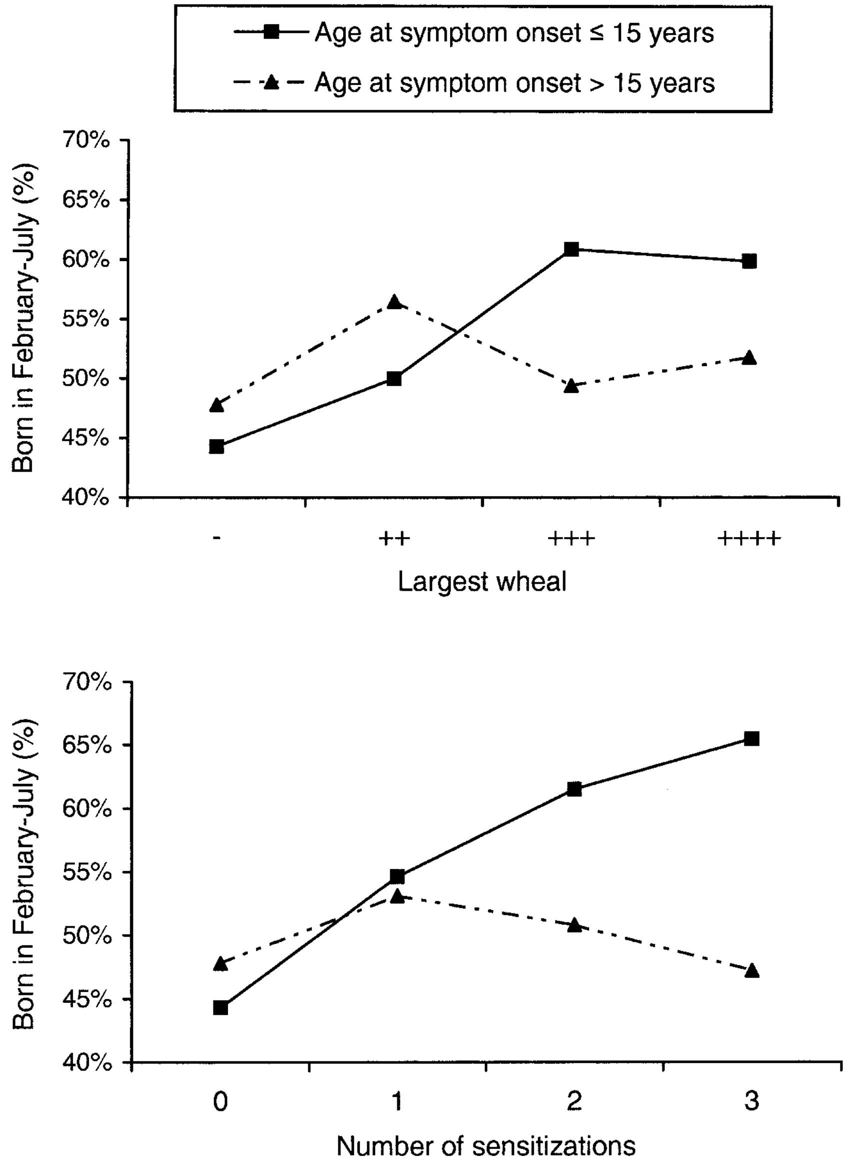

Figure 3. *Proportion of subjects born in February–July for the groups with age at symptom onset ≤15 years and >15 years, according to the dimension of the largest wheal (upper graph) and to the number of sensitizations (lower graph). The "number of sensitizations" refers to the total number of main pollen mixes with a positive wheal. Only 11 patients showed onset of symptoms ≤15 years and largest wheal equal to +. They were excluded from the figure for the small sample size, although they were still included in the statistical analysis.*

The validity of the association we found between birth in pollen season and pollen sensitization is supported by several factors. First, our results refer to patients sensitized only to pollens. Sensitization to perennial allergens, in fact, has been associated with birth during other periods of the year,[4,8,12] and its presence among pollinosis patients could have masked the actual association with pollen season. Second, based on the pollen count and our specific hypothesis, we avoided multiple statistical comparisons for every month and every combination of months. In this way, we reduced the likelihood of committing a type I error (i.e., to find an association by chance where an association does not actually exist). Finally, we found a significant dose–response relationship (the association got stronger as the degree of allergic reactivity to pollens increased) that is considered a main epidemiologic criterion for assessing causality.[26] Moreover, although the percentage of subjects born in any of the pollen season months was higher for SPT-positive than SPT-negative patients, this effect was much stronger in the months of February and March. It is noteworthy that subjects born in February or March were exposed to massive doses of pollens longer than subjects born at the end of the pollen season.

By using symptomatic SPT-negative patients, rather than a sample from the general population, as our control group, we could avoid potential misclassification related to the presence of sensitized subjects in the general population. Moreover, because both cases and controls were affected by

TABLE V

The Effect of Clinical and Demographic Variables on the Relationship between Birth in Pollen Season and HR Pollen Sensitization

Variables	Born in Feb–July	Born in Aug–Jan	Effect Modification			Confounding
			OR	95% CI	Test of Homogeneity	Crude OR/ Adjusted OR
Age of onset					0.026	1.38/1.35
≤15 years						
Cases	179	118	1.91	1.32–2.77		
Controls	81	102				
>15 years						
Cases	219	211	1.13	0.87–1.48		
Controls	213	233				
Gender					0.587	1.38/1.40
Male						
Cases	203	181	1.31	0.95–1.81		
Controls	113	132				
Female						
Cases	195	148	1.48	1.10–1.98		
Controls	181	203				
Symptoms					0.788	1.38/1.35
Asthma						
Cases	14	15	1.28	0.56–2.96		
Controls	40	55				
Rhinitis						
Cases	188	156	1.26	0.93–1.71		
Controls	162	170				
Asthma + Rhinitis						
Cases	196	158	1.48	1.05–2.10		
Controls	92	110				
Duration of symptoms					0.991	1.38/1.37
≤1 year						
Cases	82	71	1.34	0.89–2.04		
Controls	97	113				
2–4 years						
Cases	168	129	1.35	0.95–1.94		
Controls	99	103				
>4 years						
Cases	148	129	1.39	0.97–1.99		
Controls	98	119				

See Statistical Methods and Results.

asthma and/or rhinitis, we controlled the potential confounding effect of the respiratory symptoms, that have been shown themselves to be associated with birth at specific times of the year.[16–18] The age at symptom onset proved to be an effect modifier in the association between birth in pollen season and pollen sensitization, because the association was significant only in the group of patients with an early onset of symptoms (first 15 years of life).

These findings are consistent with those from previous studies. In a study carried out in London, Sibbald et al.[22] found a significant association between birth in May–June and rhinitis only among patients with an early onset of symptoms (≤20 years). Similarly, in a Finnish study,[7] the risk of developing sensitization to birch pollen was associated with being born in February–April, but the month of birth no longer appeared to affect the risk in the age group over 20 years. In Sweden, Åberg[23] showed that the effect of birth season on allergic rhinitis was stronger among children with onset of symptoms early in school years and it was not present any more after the first 10 years of life.

In our retrospective study design, it is difficult to distinguish the effect of the age at the time of the visit from that of the age at symptom onset because the two variables are highly correlated. More than 70% of our patients, in fact, were seen in the medical center within 5 years from the onset of the disease. Nevertheless, among pollinosis patients, the likelihood of being born in pollen season correlated more closely with the age at symptom onset than the age at visit. Consequently, we chose to stratify the data according to the age at symptom onset.

Although, in our statistical analysis, we chose 15 years as a cut-off point for defining an early onset of symptoms, Fig. 2 suggests that a linear relationship between age and birth during pollen season is probably present among pollinosis patients. The probability of having been born in February–July, in fact, seems to gradually decrease as the age at symptom onset increases. Our data suggest that the exposure to allergens in the first months of life is a risk factor for developing an allergic sensitization at a young age. If the allergic sensitization does not occur at a young age, the effect of the season of birth appears to decrease over time and to become completely irrelevant for developing allergy after the age of 30.

Although little is known on the natural history of allergic sensitization, it is possible that the type and level of the sensitizations of some of our patients, especially the older ones, have changed over time. Some allergic patients could have had negative SPT in the past and vice versa, leading to a misclassification in older age. Due to the retrospective nature of our data, we cannot exclude that this potential misclassification is a reason why the association between birth in pollen season and allergic sensitization was not found among old patients.

In conclusion, a significant association between birth in pollen season and pollen sensitization was found, and it correlated with the level of allergic reactivity to pollens. The association was valid only among patients with onset of allergic symptoms in the first 15 years of life.

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