

Month of birth, atopic disease, and sensitization to common aeroallergens in Greece

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The aim of the study was to evaluate the influence of the month of birth on the development of atopic disease and the rate of sensitization to common environmental allergens in Greece. Analysis of the month of birth of 1755 individuals with atopic disease (asthma, rhinitis, atopic dermatitis), out of whom 771 had positive skin tests/RAST to *Dermatophagoides pteronyssinus* and mixed grasses, in comparison to total live births (2 877 733) in Greece during 1968–88, was performed and showed significant correlation ($p < 0.001$) between month of birth and development of atopic disease in general. Months of birth May to August correlated best with bronchial asthma ($p < 0.05$) and rhinitis ($p < 0.05$), and July to August with atopic dermatitis ($p < 0.05$). Significantly greater than the expected frequency was found for *D. pteronyssinus* sensitivity for months of birth May to August ($p < 0.01$), for mixed grass pollen March to August ($p < 0.01$), and for *Olea europaea* pollen mainly March ($p < 0.05$). Our results indicate that in Greece high-risk birth months for development of atopy are May to August, whereas for sensitization to common aeroallergens they are March for *O. europaea*, March to August for mixed grasses, and May to August for *D. pteronyssinus*.

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The occurrence of atopic disease is known to depend on both genetic and environmental factors (1). It has also been suggested that the first few months of life constitutes a sensitive period during which exposure to certain allergens may predispose to the subsequent development of atopic disease (2, 4), especially in individuals with genetic predisposition (5). The quantity of the allergen is also essential, and there is evidence that exposure to high quantities of allergen during infancy is associated with increased risk of sensitization to this kind of allergen and to development of atopy later in life (6).

If this hypothesis is correct, a relationship between the month of birth and sensitization to common allergens and subsequent development of atopic disease would be expected, as most of these allergens show seasonal variation. During the last 15 years, several investigators from different countries showed a statistically significant association between the month of birth and the risk of immediate hypersensitivity (2, 6, 7–10), although a few old studies failed to confirm this (11–13).

We report here the results of a study in which we examined the relationship between month of birth

and development of atopic disease and rate of sensitization to common aeroallergens in Greece.

Material and methods

Study group

We examined retrospectively the records of 1755 patients aged 2.5–20 years (mean age: 7 years, SD: 4.40) with atopic disease, who had visited the Department of Allergology in the University Children's Hospital "P. & A. Kyriakou" between 1981 and 1988. Atopic disease was defined as a history of bronchial asthma, atopic eczema/dermatitis, or allergic rhinitis/rhinoconjunctivitis. In a few cases, gastrointestinal allergy or urticaria was included when there was no obvious inciting factor.

The subjects comprised 1078 boys and 677 girls (group A), all born in Greece between 1968 and 1988. Among them, 1352 were affected by asthma (group B), 350 by atopic dermatitis (group C), and 677 by rhinitis (group D). Most of them had elevated serum IgE. Reference values for age and sex were derived from performance of distribution curves of total serum IgE in Greek children (14). A total of 771 indi-

Table 1. Month-of-birth distribution of controls (Greek population born 1968–88) and patients with atopy, asthma, atopic dermatitis, and rhinitis, and *D. pteronyssinus* (D. pt.), mixed grass pollens, and *Olea europaea* skin test positivity

Month of birth	Controls (no.)	Atopy (no.)	Asthma (no.)	Atopic dermatitis (no.)	Rhinitis (no.)	D. pt. (no.)	Mixed grasses (no.)	<i>Olea europaea</i> (no.)
January	249 840	134	103	35	44	19	20	19
February	228 845	109	85	26	45	15	20	12
March	252 269	154	122	35	60	24	39	26
April	237 345	143	108	26	56	18	30	14
May	253 197	174	133	26	82	28	38	16
June	247 524	164	123	32	60	25	32	19
July	257 125	200	145	46	63	32	39	20
August	247 336	195	152	40	71	33	34	21
September	234 847	139	108	25	55	21	19	7
October	238 283	126	101	25	53	19	22	3
November	221 875	108	84	17	41	12	16	12
December	209 227	109	88	17	37	10	15	12
Total	2 877 733	1755	1352	350	667	56	324	191
		χ^2 : 48.34 $P < 0.001$	χ^2 : 30.74 $P < 0.01$	χ^2 : 20.21 $P < 0.05$	χ^2 : 22.35 $P < 0.05$	χ^2 : 20.54 $P < 0.05$	χ^2 : 25.92 $P < 0.01$	χ^2 : 14.42 $P = \text{NS}$

χ^2 : chi-square test.

viduals had positive skin prick test to *Dermatophagoides pteronyssinus* (D. pt.) (group E), mixed grasses (group F), and *Olea europaea* (group G), which constitute the commonest aeroallergens in Greece.

Prick tests were done with a panel of 40 common environmental allergens (Bencard, UK) on the volar surface of the forearm. *In vitro* specific IgE was determined to various allergens with the radioallergen sorbent test (RAST) (Pharmacia, Sweden) and graded from 0 to 4. Patients were considered positive only when the RAST reaction was ≥ 2 and/or when Prick test reaction was equal to or greater than the positive (histamine 1 mg/ml) control (wheal diameter ≥ 4 mm). The study was approved by the ethics committee of our hospital. Since the individuals of the group concerned were born in the years 1968–88, their month-of-birth distribution was compared with the distribution of the total live births in Greece in the same interval (2 877 733), as recorded by the National Statistical Society of Greece (15). The number of patients expected to have a given month of birth was calculated as the ratio between the number of persons born in that month and the total number of births times the number of patients.

Statistical analysis

Statistical analysis was performed with the chi-square test as a goodness of fit test and the chi-square test with Yates (continuity) correction.

The relative risk, R_j , of developing immediate hypersensitivity to an allergen in persons born in period j was estimated with the equation

$$R_j = \frac{n_j/n}{N_j/N}$$

where n is the total number of patients born in period j of whom n_j are sensitive to the allergen, and N_j and N are the corresponding numbers in the reference group. With this definition, the risk in the total patient group (n) was 1 (3). Confidence intervals (CI) for relative risks were also calculated (16).

Results

As shown in Table 1, the monthly live birth distribution in Greece was significantly different from the monthly distribution of each of the above groups, with the exception of group G (*O. europaea*), where the total number of subjects was very small.

A significantly higher proportion of persons with atopy were born from May to August compared to the rest of the year. The increased prevalence of atopic persons born in this period corresponded to a relative risk of 0.19 (Table 2). Similarly, the months of birth May to August correlated best with asthma and rhinitis with corresponding relative risks of 1.17 and 1.18, respectively, while more of the patients with atopic dermatitis were born in July and August (relative risk: 1.40) (Table 2).

In comparison of the two trimesters with the ap-

Table 2. Observed and expected no. of persons with atopic disease born in certain period and corresponding relative risk for same period

	Months of birth	Observed/expected no.	df=1	Chi-square test	p value	Relative risk	95% CI
Atopy	May–August	733/613	36.07		<0.001	1.19	1.09–1.30
Asthma	May–August	533/472	21.21		<0.001	1.17	1.06–1.29
Rhinitis	May–August	276/233	12.2		<0.001	1.18	1.03–1.36
Dermatitis	July–August	86/61	12		<0.001	1.40	1.11–1.75

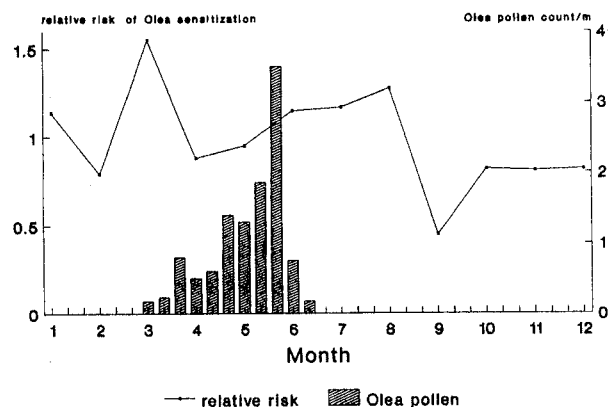


Fig. 1. Trimester with highest risk of sensitization to *Olea europaea* precedes period with highest *Olea* pollen counts in Greece.

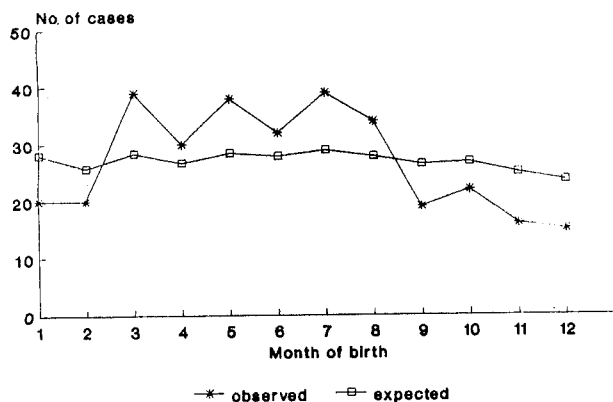


Fig. 2. Observed and expected frequency of sensitization to mixed pollens in Greece.

parently highest (February–April) and lowest (September–November) risk of sensitization to *O. europaea*, a statistically significant difference was observed (chi-square: 4.12, $p < 0.05$). Interestingly, these three months (February, March, April) precede the period with the highest *Olea* pollen counts in Greece (17) (Fig. 1). Moreover, the month of birth with the highest relative risk of sensitization to *O. europaea* was found to be March (relative risk: 1.55, 95% CI: 1.03–2.33); this means, for example, that persons born in March and consequently exposed to high *Olea* pollen counts during the following trimester have a 55% higher risk of sensitization to *O. europaea*, compared with persons born in the rest of the year.

Similarly, a greater incidence of mixed pollens sensitization than the expected was shown for patients born between March and August (chi-square: 23.61, $p < 0.001$) (Fig. 2), with a corresponding relative risk of 1.26 (95% CI: 1.06–1.5). House-dust-mite-positive patients showed a significantly higher proportion of births in the months May to August (chi-square: 14.04, $p < 0.001$), corresponding to a

relative risk of 1.31 (95% CI: 1.06–1.63). In a previous study (18), the months with the highest concentration of *D. pt.* measured in house dust samples in the area of Attiki, Greece, were found to be August to December, i.e., the months following the high-risk birth period (Fig. 3).

Discussion

There is increasing experimental and clinical evidence that the first few months of life constitute a time of increased risk of primary sensitization to aeroallergens. Early infancy seems to be the period when specific T-cell response can determine whether an allergic reactivity will occur in later life or not (19–21).

Several investigators looked for a correlation between the month of birth and the risk of developing atopy. Although initial studies failed to identify any relationship (11–13), many recent studies appear to correlate a significant clustering of certain months of birth with IgE sensitization to common allergens (e.g., grass mite, ragweed, birch) and subsequently with development of allergy (2–10).

Our results agree with most of these studies (taking into account the climatic differences) and correspond particularly well to findings from Italy (7), probably because of the geographic closeness of the two countries. They demonstrate a significantly increased risk of sensitization to pollens in those born in March to August. These months correspond roughly to periods before the blooming season in Greece (which is spring and autumn for mixed pollens) (22). Especially for *O. europaea*, it is known that in Greece, the peak of blooming is reached during the month of May (March–June) (15), and the month of birth with the highest risk of sensitization to pollen was found to be March. The second lower peak which was observed during summer (June–August) is most probably due to (cross reaction)

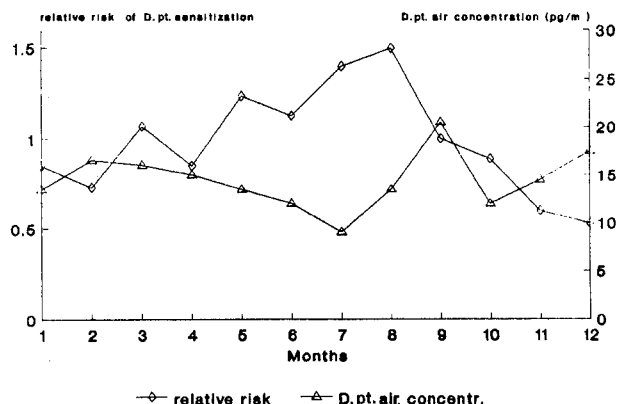


Fig. 3. High-risk birth period for sensitization to *D. pt.* (—◇—) precedes months with highest concentration of *D. pt.* measured in house dust samples (—△—).

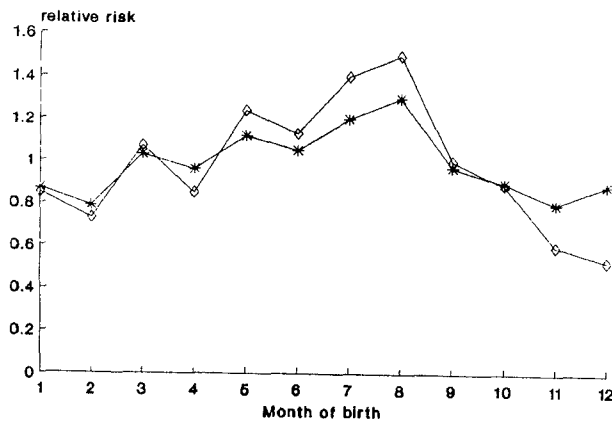


Fig. 4. Months of highest risk of development of asthma (*-*) were same as those for sensitization to *D. pt.* (-◇-).

multiple sensitization to the other pollens.

Patients with sensitivity to *D. pt.* were born predominantly in the period May–August. The highest concentrations of mite are observed between August and December (18). The months of the highest risk of development of asthma and/or rhinitis were the same as those for sensitization to *D. pt.* (Fig. 4). Moreover, the variations in the relative risk of *D. pt.* positivity and development of asthma in relation with the month of birth showed a great similarity (Fig. 4). These findings support recent studies showing a relationship between the levels of aeroallergens during children's month of birth and development of asthma (23), as well as a strong association between exposure to high concentration of house-dust mite in infancy and development of asthma in childhood (5).

In conclusion, our study supports the hypothesis that the environmental conditions encountered in infancy are of great importance for the future development of allergic disease. Whether or not family planning by selection of a month of conception to avoid high-risk periods would be worthwhile as a preventive measure is not clear. However, in Finland, it has been estimated that if all children were born in July or August (the months most favorable to prevention of pollen allergy), the prevalence of pollen allergy in children and young adults would be reduced by approximately 25% (23).

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