

‘Horoscope effect’ not only for seasonal but also for non-seasonal allergens

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Summary

We report on the relation between the month of birth and the chance of developing an IgE antibody response as found in a study sample of 150000 subjects. Our results confirm that for the three seasonal allergens birch pollen, grass pollen and house dust mite, an increased relative risk was found for subjects born up to 3 months before the main season for that allergen in The Netherlands. For cat and dog allergy an increased relative risk was found from November to January, perhaps reflecting increased exposure to these pets during the winter. Surprisingly, however, also for egg white and cow's milk a clearly increased relative risk was found from November to January and a decreased relative risk in May. These data support the hypothesis of a ‘sensitive’ period in the first months of life during which allergen exposure is more likely to prime for an allergy later in life. The results with the non-seasonal allergens suggest that another seasonal factor exists which early in life assists (or prevents) priming by allergen.

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Introduction

For the development of IgE-mediated allergy both hereditary factors and environmental factors are important. Despite the fact that allergies (particularly inhalation allergies) do not usually become apparent until after several years of allergen exposure, there are several reports indicating that allergen contact during the first months of life may increase the risk of developing an allergy later in life. Most of these reports [1–7] were not universally accepted, probably because the effects found were small (relative risks < 2), the calculations were based on relatively small numbers (less than 100 positive cases per month of birth) and often no correction was made for the multiple comparisons involved when testing for differences between each of the 12 months.

An additional complication was the observation made by Sibbald and Rink [8] that not only for atopic rhinitis, but also for non-atopic rhinitis a birth month variation was found. This finding suggested that the effect observed by scoring clinical symptoms might not be purely a reflection of the risk of developing IgE antibodies.

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Another potentially confounding issue is the birth month variation found for some other diseases like diabetes mellitus, which are possibly related to spring restoration of the ovulatory pattern [9]. An excess of diabetes births during the first quarter and a deficiency during the last quarter were found.

In a preliminary study [10] we used the results of diagnostic IgE antibody tests obtained in one year (1986) to objectively establish the two periods of three consecutive months that were the ‘high season’ and the ‘low season’, respectively, for that study sample. Next, we analysed the results of the IgE antibody tests obtained in 1987 using the ‘seasons’ as defined based on the 1986 data. The results provided statistical support for a month-of-birth effect for grass pollen, house dust mite and dog, whereas the effect for cat was not significant.

This analysis convinced us that at least for some allergens a season-of-birth effect exists, but did not give accurate information on the duration of the period. Furthermore, although increased exposure to household pet allergens in wintertime seemed plausible, the suggestion that seasonal exposure to allergen is the main factor was weakened by the results for the dog allergen: in contrast to the dust mite allergen level, the dog allergen level in house dust does not show a clear seasonal

Table 1. The cut-off value used to classify a serum as strongly positive was 10% of input anti-IgE bound for the food allergens and 20% of input anti-IgE bound for the inhalant allergens. Weakly positive patients were counted as negative.

Allergen	'High season'	Total number	Strongly positive	Percentage in 'high season'		Relative risk	95% confidence interval	
				(-) sera	(+) sera			
Birch	Nov-Apr	72 648	2917	48.32	54.37	1.125	1.087	1.164
Grass	Dec-May	153 323	16 459	49.26	52.51	1.066	1.050	1.083
Mite	May-Oct	155 863	30 816	50.72	53.86	1.062	1.050	1.074
Cat	Sep-Feb	154 482	9131	48.45	50.99	1.052	1.031	1.075
Dog	Sep-Feb	153 854	4035	48.47	54.08	1.116	1.084	1.148
Egg	Sep-Feb	78 246	1740	48.70	59.02	1.212	1.165	1.261
Milk	Sep-Feb	89 316	2231	48.63	53.74	1.105	1.063	1.149

variation (data not shown). We therefore analysed a considerably larger data set and included two non-seasonal allergens (egg and milk) as well as a third seasonal allergen (birch pollen).

Materials and methods

Results of the diagnostic IgE antibody tests that we performed in the period 1983-1990 were analysed. The majority of the sera were tested on a panel of allergens that included grass pollen, house dust mite (*Dermatophagoides pteronyssinus*), cat dander and dog dander. Children below the age of 4 were tested in addition for IgE to cow's milk and egg white, whereas patients over this age were tested for IgE to birch pollen. The actual numbers of tests analysed for each allergen are indicated in Table 1. For the analysis we focused on strongly positive reactions only: the cut-off value used here was considerably higher than our usual cut-off value of 2% of input anti-IgE bound which corresponds to approximately 0.5 µg IgE antibody/l. We used for the food allergens 10% of input anti-IgE bound (3 µg/l) and for the inhalant allergens 20% of input anti-IgE bound (10 µg/l). Based on these cut-off values approximately 50% of the positive patients are strongly positive. For patients that were tested several times we used only the highest test result for each allergen. Patients that were positive for more than one allergen were not excluded.

When we scrutinized the data files for inconsistencies or errors, we found an excess of patients stated to be born on the 1st of January. For the majority of these patients the actual date of birth was unknown, a problem usually related to the patient's ethnic background. For the current analysis we therefore deleted all patients born on January 1st.

Neither of these two points (selection of a high cut-off value and deletion of patients born on January 1st) had a major effect on the final analysis.

Results

The results of the statistical analysis, expressed as relative risk for each month, are shown in Fig. 1. The birch pollen provided a good internal control for the house dust mite, because the two are very close to being mirror images. This makes it quite unlikely that the overall results are due to a hidden bias. The results for the food allergens were unexpected but striking, particularly for egg white. The results for cat allergen (not shown in the figure) were very similar to dog allergen, but less marked. The four not-so-clearly-seasonal allergens cat, dog, egg and milk have very similar season-of-birth patterns.

As far as cat and dog allergen exposure is concerned, seasonal variation is possible, since indoor exposure may be higher during the winter. In preliminary analyses we did not, however, find a significant increase in cat allergen levels in house dust during the winter.

In Table 1 we show the results of the statistical analysis when for each allergen a period of six consecutive months 'high season' was contrasted with the remaining 6 months 'low season'.

Discussion

It is clear from the analysis in Table 1 that the practical value of these findings in terms of allergy prevention by birth planning is negligible: even in the most extreme example (egg) only 59% of the patients were born in 'high season'. The relevance of these findings is rather in the

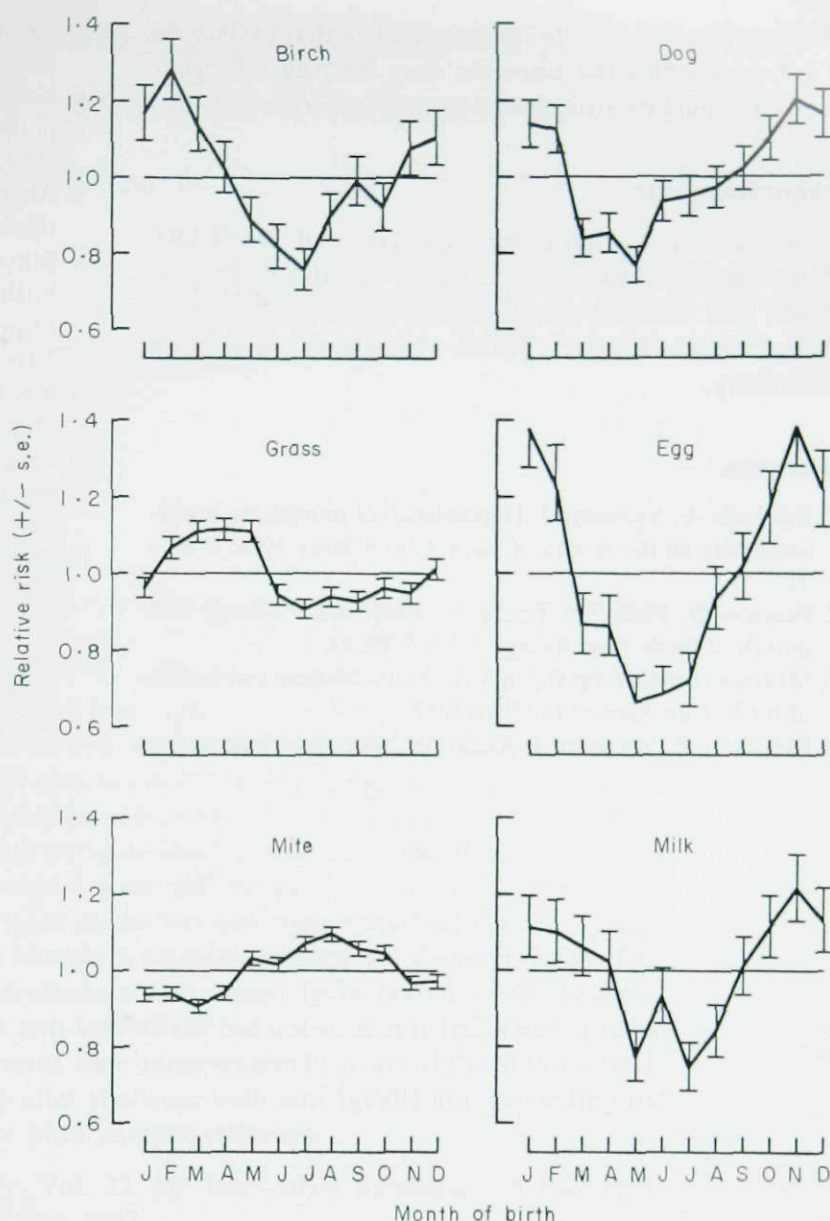


Fig. 1. The month of birth influences the chance of developing IgE antibodies to the indicated allergens. The relative risk is calculated as (number of positive cases born in that month/total number of patients born in that month)/(number of positive cases not born in that month/total number of patients not born in that month). Three seasonal allergens are on the left: birch pollen (allergen peak in March–April), grass pollen (allergen peak in June) and house dust mite (allergen peak in September).

elucidation of the mechanism of allergic sensitization. Three points of interest are:

- 1 The results with the three seasonal allergens suggest that allergen exposure during the first few months of life increases the risk of developing an allergy.
- 2 The actual appearance of IgE antibodies is usually many years later; this suggests an effect on antigen-specific regulatory mechanisms rather than on IgE antibody production itself. However, from the presented data it cannot be excluded that the effect of allergen exposure is later in life, e.g. at the age of 12–15 months or 24–27 months rather than at 0–3 months, particularly if one considers the possibility that paediatric vaccination schedules are rigid: the increased risk of sensitization might reflect the effect of allergen exposure at the time of vaccination.

- 3 The results with the 'non-season' allergens suggest that in addition to allergen exposure another seasonal factor contributes. If this cofactor works acutely, it peaks in November (if it is an adjuvant cofactor) or in May (if it is a suppressive cofactor). Viruses are obvious candidates as adjuvant cofactor because of the claimed positive associations between viral infections and the development of allergies [9], but also as suppressive cofactors because of the possibility of suppressive effects of interferon on IgE synthesis. Physical factors might also be implicated, such as a hypothetical protective effect of sunlight or negative effects of central heating on the airway mucosal membranes.

Classical immunology teaches that exposure of an immature immune system to antigens is likely to induce

tolerance. The 'horoscope' effect indicates that in the case of IgE antibodies the opposite may be true: allergen-specific priming of the immune system by early exposure.

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References

- 1 Björkstén F, Suoniemi I. Dependence of immediate hypersensitivity on the month of birth. *Clin Allergy* 1976; 6:165-71.
- 2 Pearson D, Freed D, Taylor G. Respiratory allergy and month of birth. *Clin Allergy* 1977; 7:29-33.
- 3 Morrison Smith J, Springett VH. Atopic disease and month of birth. *Clin Allergy* 1979; 9:153-7.
- 4 Björkstén F, Suoniemi I, Koski V. Neonatal birch pollen contact and subsequent allergy to birch pollen. *Clin Allergy* 1980; 10:585-91.
- 5 Korsgaard J, Dahl R. Sensitivity to house-dust mite and pollen in adults. Influence of month of birth. *Clin Allergy* 1983; 13:528-36.
- 6 Åberg N. Birth season variation in asthma and allergic rhinitis. *Clin Allergy* 1989; 19:643-8.
- 7 Businco L, Cantani A, Farinella F, Businco E. Month of birth and grass pollen or mite sensitization in children with respiratory allergy: a significant relationship. *Clin Allergy* 1988; 18:269-74.
- 8 Sibald B, Rink E. Birth month variation in atopic and non-atopic rhinitis. *Clin Exp Allergy* 1990; 20:285-8.
- 9 Jongbloet PH, Van Soestbergen M, Van der Veen EA. Month-of-birth distribution of diabetics and ovopathy: a new aetiological view. *Diab Res* 1988; 9: 51-8.
- 10 De Groot H, Stapel SO, Aalberse RC. Statistical analysis of IgE antibodies to the common inhalent allergens in 44,496 sera. *Ann Allergy* 1990; 65:97-104.
- 11 Frick OL, German DF, Mills J. Development of allergy in children association with virus infections. *J Allergy Clin Immunol* 1979; 63:228-41.

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